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1.	Your reference	AST19
2.	Patent application number *(The Patent Office will fill in this part)*	24 OCT 2003 0324919.0
3.	Full name, address and postcode of the or each applicant *(underline all surnames)* 08118317002	Astex Technology Limited 436 Cambridge Science Park Milton Road Cambridge CB4 0QA United Kingdom
	Patents ADP number *(if you know it)*	
	If the applicant is a corporate body, give the country/state of its incorporation	United Kingdom
4.	Title of the invention	PHARMACEUTICAL COMPOUNDS
5.	Name of your agent (if you have one) "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	M. R. Hutchins & Co 33 Connaught Way Tunbridge Wells TN4 9QP 08443293001
	Patents ADP number *(if you know it)*	C81430
6.	If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number	Country / Priority application number *(if you know it)* / Date of filing *(day/month/year)*
7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application / Date of filing *(day/month/year)*
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Priority documents	
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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	1
Request for substantive examination *(Patents Form 10/77)*	
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11. I/We request the grant of a patent on the basis of this application

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12. Name and daytime telephone number of person to contact in the United Kingdom

Dr Michael R. Hutchins
01892 539659

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PHARMACEUTICAL COMPOUNDS

This invention relates to pyrazole compounds that inhibit or modulate the activity of cyclin dependent kinases (CDK), to the use of the compounds in the treatment or prophylaxis of disease states or conditions mediated by cyclin dependent kinases, and to novel compounds having cyclin dependent kinase inhibitory or modulating activity. Also provided are pharmaceutical compositions containing the compounds and novel chemical intermediates.

Background of the Invention

Protein kinases constitute a large family of structurally related enzymes that are responsible for the control of a wide variety of signal transduction processes within the cell (Hardie, G. and Hanks, S. (1995) *The Protein Kinase Facts Book. I and II*, Academic Press, San Diego, CA). The kinases may be categorized into families by the substrates they phosphorylate (e.g., protein-tyrosine, protein-serine/threonine, lipids, etc.). Sequence motifs have been identified that generally correspond to each of these kinase families (e.g., Hanks, S.K., Hunter, T., *FASEB J.*, 9:576-596 (1995); Knighton, *et al.*, *Science*, 253:407-414 (1991); Hiles, *et al.*, *Cell*, 70:419-429 (1992); Kunz, *et al.*, *Cell*, 73:585-596 (1993); Garcia-Bustos, *et al.*, *EMBO J.*, 13:2352-2361 (1994)).

Protein kinases may be characterized by their regulation mechanisms. These mechanisms include, for example, autophosphorylation, transphosphorylation by other kinases, protein-protein interactions, protein-lipid interactions, and protein-polynucleotide interactions. An individual protein kinase may be regulated by more than one mechanism.

Kinases regulate many different cell processes including, but not limited to, proliferation, differentiation, apoptosis, motility, transcription, translation and other signalling processes, by adding phosphate groups to target proteins. These phosphorylation events act as molecular on/off switches that can modulate or regulate the target protein biological function. Phosphorylation of target proteins

occurs in response to a variety of extracellular signals (hormones, neurotransmitters, growth and differentiation factors, etc.), cell cycle events, environmental or nutritional stresses, etc. The appropriate protein kinase functions in signalling pathways to activate or inactivate (either directly or indirectly), for example, a metabolic enzyme, regulatory protein, receptor, cytoskeletal protein, ion channel or pump, or transcription factor. Uncontrolled signalling due to defective control of protein phosphorylation has been implicated in a number of diseases, including, for example, inflammation, cancer, allergy/asthma, disease and conditions of the immune system, disease and conditions of the central nervous system, and angiogenesis.

The process of eukaryotic cell division may be broadly divided into a series of sequential phases termed G1, S, G2 and M. Correct progression through the various phases of the cell cycle has been shown to be critically dependent upon the spatial and temporal regulation of a family of proteins known as cyclin dependent kinases (cdks) and a diverse set of their cognate protein partners termed cyclins. Cdks are cdc2 (also known as cdk1) homologous serine-threonine kinase proteins that are able to utilise ATP as a substrate in the phosphorylation of diverse polypeptides in a sequence dependent context. Cyclins are a family of proteins characterised by a homology region, containing approximately 100 amino acids, termed the "cyclin box" which is used in binding to, and defining selectivity for, specific cdk partner proteins.

Modulation of the expression levels, degradation rates, and activation levels of various cdks and cyclins throughout the cell cycle leads to the cyclical formation of a series of cdk/cyclin complexes, in which the cdks are enzymatically active. The formation of these complexes controls passage through discrete cell cycle checkpoints and thereby enables the process of cell division to continue. Failure to satisfy the pre-requisite biochemical criteria at a given cell cycle checkpoint, *i.e.* failure to form a required cdk/cyclin complex, can lead to cell cycle arrest and/or cellular apoptosis. Aberrant cellular proliferation, as manifested in cancer, can often be attributed to loss of correct cell cycle control. Inhibition of cdk enzymatic

activity therefore provides a means by which abnormally dividing cells can have their division arrested and/or be killed. The diversity of cdks, and cdk complexes, and their critical roles in mediating the cell cycle, provides a broad spectrum of potential therapeutic targets selected on the basis of a defined biochemical rationale.

Progression from the G1 phase to the S phase of the cell cycle is primarily regulated by cdk2, cdk3, cdk4 and cdk6 via association with members of the D and E type cyclins. The D-type cyclins appear instrumental in enabling passage beyond the G1 restriction point, where as the cdk2/cyclin E complex is key to the transition from the G1 to S phase. Subsequent progression through S phase and entry into G2 is thought to require the cdk2/cyclin A complex. Both mitosis, and the G2 to M phase transition which triggers it, are regulated by complexes of cdk1 and the A and B type cyclins.

During G1 phase Retinoblastoma protein (Rb), and related pocket proteins such as p130, are substrates for cdk(2, 4, & 6)/cyclin complexes. Progression through G1 is in part facilitated by hyperphosphorylation, and thus inactivation, of Rb and p130 by the cdk(4/6)/cyclin-D complexes. Hyperphosphorylation of Rb and p130 causes the release of transcription factors, such as E2F, and thus the expression of genes necessary for progression through G1 and for entry into S-phase, such as the gene for cyclin E. Expression of cyclin E facilitates formation of the cdk2/cyclin E complex which amplifies, or maintains, E2F levels via further phosphorylation of Rb. The cdk2/cyclin E complex also phosphorylates other proteins necessary for DNA replication, such as NPAT, which has been implicated in histone biosynthesis. G1 progression and the G1/S transition are also regulated via the mitogen stimulated Myc pathway, which feeds into the cdk2/cyclin E pathway. Cdk2 is also connected to the p53 mediated DNA damage response pathway via p53 regulation of p21 levels. p21 is a protein inhibitor of cdk2/cyclin E and is thus capable of blocking, or delaying, the G1/S transition. The cdk2/cyclin E complex may thus represent a point at which biochemical stimuli from the Rb, Myc and p53 pathways are to some degree integrated. Cdk2 and/or the cdk2/cyclin E complex therefore

represent good targets for therapeutics designed at arresting, or recovering control of, the cell cycle in aberrantly dividing cells.

The exact role of cdk3 in the cell cycle is not clear. As yet no cognate cyclin partner has been identified, but a dominant negative form of cdk3 delayed cells in G1, thereby suggesting that cdk3 has a role in regulating the G1/S transition.

Although most cdks have been implicated in regulation of the cell cycle there is evidence that certain members of the cdk family are involved in other biochemical processes. This is exemplified by cdk5 which is necessary for correct neuronal development and which has also been implicated in the phosphorylation of several neuronal proteins such as Tau, NUDE-1, synapsin1, DARPP32 and the Munc18/Syntaxin1A complex. Neuronal cdk5 is conventionally activated by binding to the p35/p39 proteins. Cdk5 activity can, however, be deregulated by the binding of p25, a truncated version of p35. Conversion of p35 to p25, and subsequent deregulation of cdk5 activity, can be induced by ischemia, excitotoxicity, and β-amyloid peptide. Consequently p25 has been implicated in the pathogenesis of neurodegenerative diseases, such as Alzheimer's, and is therefore of interest as a target for therapeutics directed against these diseases.

Cdk7 is a nuclear protein that has cdc2 CAK activity and binds to cyclin H. Cdk7 has been identified as component of the TFIIH transcriptional complex which has RNA polymerase II C-terminal domain (CTD) activity. This has been associated with the regulation of HIV-1 transcription via a Tat-mediated biochemical pathway. Cdk8 binds cyclin C and has been implicated in the phosphorylation of the CTD of RNA polymerase II. Similarly the cdk9/cyclin-T1 complex (P-TEFb complex) has been implicated in elongation control of RNA polymerase II. PTEF-b is also required for activation of transcription of the HIV-1 genome by the viral transactivator Tat through its interaction with cyclin T1. Cdk7, cdk8, cdk9 and the P-TEFb complex are therefore potential targets for anti-viral therapeutics.

At a molecular level mediation of cdk/cyclin complex activity requires a series of stimulatory and inhibitory phosphorylation, or dephosphorylation, events. Cdk

phosphorylation is performed by a group of cdk activating kinases (CAKs) and/or kinases such as wee1, Myt1 and Mik1. Dephosphorylation is performed by phosphatases such as cdc25(a & c), pp2a, or KAP.

Cdk/cyclin complex activity may be further regulated by two families of endogenous cellular proteinaceous inhibitors: the Kip/Cip family, or the INK family. The INK proteins specifically bind cdk4 and cdk6. $p16^{ink4}$ (also known as MTS1) is a potential tumour suppressor gene that is mutated, or deleted, in a large number of primary cancers. The Kip/Cip family contains proteins such as $p21^{Cip1,Waf1}$, $p27^{Kip1}$ and $p57^{kip2}$. As discussed previously p21 is induced by p53 and is able to inactivate the cdk2/cyclin(E/A) and cdk4/cyclin(D1/D2/D3) complexes. Atypically low levels of p27 expression have been observed in breast, colon and prostate cancers. Conversely over expression of cyclin E in solid tumours has been shown to correlate with poor patient prognosis. Over expression of cyclin D1 has been associated with oesophageal, breast, squamous, and non-small cell lung carcinomas.

The pivotal roles of cdks, and their associated proteins, in co-ordinating and driving the cell cycle in proliferating cells have been outlined above. Some of the biochemical pathways in which cdks play a key role have also been described. The development of monotherapies for the treatment of proliferative disorders, such as cancers, using therapeutics targeted generically at cdks, or at specific cdks, is therefore potentially highly desirable. Cdk inhibitors could conceivably also be used to treat other conditions such as viral infections, autoimmune diseases and neuro-degenerative diseases, amongst others. Cdk targeted therapeutics may also provide clinical benefits in the treatment of the previously described diseases when used in combination therapy with either existing, or new, therapeutic agents. Cdk targeted anticancer therapies could potentially have advantages over many current antitumour agents as they would not directly interact with DNA and should therefore reduce the risk of secondary tumour development.

Glycogen Synthase Kinase-3 (GSK3) is a serine-threonine kinase that occurs as two ubiquitously expressed isoforms in humans (GSK3α & beta GSK3β). GSK3 has

been implicated as having roles in embryonic development, protein synthesis, cell proliferation, cell differentiation, microtubule dynamics, cell motility and cellular apoptosis. As such GSK3 has been implicated in the progression of disease states such as diabetes, cancer, Alzheimer's disease, stroke, epilepsy, motor neuron disease and/or head trauma. Phylogenetically GSK3 is most closely related to the cyclin dependent kinases (CDKs).

The consensus peptide substrate sequence recognised by GSK3 is (Ser/Thr)-X-X-X-(pSer/pThr), where X is any amino acid (at positions (n+1), (n+2), (n+3)) and pSer and pThr are phospho-serine and phospho-threonine respectively (n+4). GSK3 phosphorylates the first serine, or threonine, at position (n). Phospho-serine, or phospho-threonine, at the (n+4) position appear necessary for priming GSK3 to give maximal substrate turnover. Phosphorylation of GSK3α at Ser21, or GSK3β at Ser9, leads to inhibition of GSK3. Mutagenesis and peptide competition studies have led to the model that the phosphorylated N-terminus of GSK3 is able to compete with phospho-peptide substrate (S/TXXXpS/pT) via an autoinhibitory mechanism. There are also data suggesting that GSK3α and GSKβ may be subtly regulated by phosphorylation of tyrosines 279 and 216 respectively. Mutation of these residues to a Phe caused a reduction in *in vivo* kinase activity. The X-ray crystallographic structure of GSK3β has helped to shed light on all aspects of GSK3 activation and regulation.

GSK3 forms part of the mammalian insulin response pathway and is able to phosphorylate, and thereby inactivate, glycogen synthase. Upregulation of glycogen synthase activity, and thereby glycogen synthesis, through inhibition of GSK3, has thus been considered a potential means of combating type II, or non-insulin-dependent diabetes mellitus (NIDDM): a condition in which body tissues become resistant to insulin stimulation. The cellular insulin response in liver, adipose, or muscle tissues, is triggered by insulin binding to an extracellular insulin receptor. This causes the phosphorylation, and subsequent recruitment to the plasma membrane, of the insulin receptor substrate (IRS) proteins. Further phosphorylation of the IRS proteins initiates recruitment of phosphoinositide-3

kinase (PI3K) to the plasma membrane where it is able to liberate the second messenger phosphatidylinosityl 3,4,5-trisphosphate (PIP3). This facilitates co-localisation of 3-phosphoinositide-dedependent protein kinase 1 (PDK1) and protein kinase B (PKB or Akt) to the membrane, where PDK1 activates PKB. PKB is able to phosphorylate, and thereby inhibit, GSK3α and/or GSKβ through phosphorylation of Ser9, or ser21, respectively. The inhibition of GSK3 then triggers upregulation of glycogen synthase activity. Therapeutic agents able to inhibit GSK3 may thus be able to induce cellular responses akin to those seen on insulin stimulation. A further *in vivo* substrate of GSK3 is the eukaryotic protein synthesis initiation factor 2B (eIF2B). eIF2B is inactivated via phosphorylation and is thus able to suppress protein biosynthesis. Inhibition of GSK3, e.g. by inactivation of the "mammalian target of rapamycin" protein (mTOR), can thus upregulate protein biosynthesis. Finally there is some evidence for regulation of GSK3 activity via the mitogen activated protein kinase (MAPK) pathway through phosphorylation of GSK3 by kinases such as mitogen activated protein kinase activated protein kinase 1 (MAPKAP-K1 or RSK). These data suggest that GSK3 activity may be modulated by mitogenic, insulin and/or amino acid stimulii.

It has also been shown that GSK3β is a key component in the vertebrate Wnt signalling pathway. This biochemical pathway has been shown to be critical for normal embryonic development and regulates cell proliferation in normal tissues. GSK3 becomes inhibited in response to Wnt stimulii. This can lead to the de-phosphorylation of GSK3 substrates such as Axin, the adenomatous polyposis coli (APC) gene product and β-catenin. Aberrant regulation of the Wnt pathway has been associated with many cancers. Mutations in APC, and/or β-catenin, are common in colorectal cancer and other tumours. β-catenin has also been shown to be of importance in cell adhesion. Thus GSK3 may also modulate cellular adhesion processes to some degree. Apart from the biochemical pathways already described there are also data implicating GSK3 in the regulation of cell division via phosphorylation of cyclin-D1, in the phosphorylation of transcription factors such as c-Jun, CCAAT/enhancer binding protein α (C/EBPα), c-Myc and/or other

substrates such as Nuclear Factor of Activated T-cells (NFATc), Heat Shock Factor-1 (HSF-1) and the c-AMP response element binding protein (CREB). GSK3 also appears to play a role, albeit tissue specific, in regulating cellular apoptosis. The role of GSK3 in modulating cellular apoptosis, via a pro-apoptotic mechanism, may be of particular relevance to medical conditions in which neuronal apoptosis can occur. Examples of these are head trauma, stroke, epilepsy, Alzheimer's and motor neuron diseases, progressive supranuclear palsy, corticobasal degeneration, and Pick's disease. *In vitro* it has been shown that GSK3 is able to hyper-phosphorylate the microtubule associated protein Tau. Hyperphosphorylation of Tau disrupts its normal binding to microtubules and may also lead to the formation of intra-cellular Tau filaments. It is believed that the progressive accumulation of these filaments leads to eventual neuronal dysfunction and degeneration. Inhbition of Tau phosphorylation, through inhibition of GSK3, may thus provide a means of limiting and/or preventing neurodegenerative effects.

WO 02/34721 from Du Pont discloses a class of indeno [1,2-c]pyrazol-4-ones as inhibitors of cyclin dependent kinases.

WO 01/81348 from Bristol Myers Squibb describes the use of 5-thio-, sulfinyl- and sulfonylpyrazolo[3,4-b]-pyridines as cyclin dependent kinase inhibitors.

WO 00/62778 also from Bristol Myers Squibb discloses a class of protein tyrosine kinase inhibitors.

WO 01/72745A1 from Cyclacel describes 2-substituted 4-heteroaryl-pyrimidines and their preparation, pharmaceutical compositions containing them and their use as inhibitors of cyclin-dependant kinases (cdks) and hence their use in the treatment of proliferative disorders such as cancer, leukaemia, psoriasis and the like.

WO 99/21845 from Agouron describes 4-aminothiazole derivatives for inhibiting cyclin-dependent kinases (cdks), such as CDK1, CDK2, CDK4, and CDK6. The invention is also directed to the therapeutic or prophylactic use of pharmaceutical

compositions containing such compounds and to methods of treating malignancies and other disorders by administering effective amounts of such compounds.

WO 01/53274 from Agouron discloses as CDK kinase inhibitors a class of compounds which can comprise an amide-substituted benzene ring linked to an N-containing heterocyclic group. Although indazole compounds are not mentioned generically, one of the exemplified compounds comprises an indazole 3-carboxylic acid anilide moiety linked via a methylsulfanyl group to a pyrazolopyrimidine.

WO 01/98290 (Pharmacia & Upjohn) discloses a class of 3-aminocarbonyl-2-carboxamido thiophene derivatives as protein kinase inhibitors. The compounds are stated to have multiple protein kinase activity.

WO 01/53268 and WO 01/02369 from Agouron disclose compounds that mediate or inhibit cell proliferation through the inhibition of protein kinases such as cyclin dependent kinase or tyrosine kinase. The Agouron compounds have an aryl or heteroaryl ring attached directly or though a CH=CH or CH=N group to the 3-position of an indazole ring.

WO 00/39108 and WO 02/00651 (both to Du Pont Pharmaceuticals) describe broad classes of heterocyclic compounds that are inhibitors of trypsin-like serine protease enzymes, especially factor Xa and thrombin. The compounds are stated to be useful as anticoagulants or for the prevention of thromboembolic disorders.

Heterocyclic compounds that have activity against factor Xa are also disclosed in WO 01/1978 Cor Therapeutics) and US 2002/0091116 (Zhu *et al.*).

WO 03/035065 (Aventis) discloses a broad class of benzimidazole derivatives as protein kinase inhibitors but does not disclose activity against CDK kinases or GSK kinases.

WO 97/36585 and US 5,874,452 (both to Merck) disclose biheteroaryl compounds that are inhibitors of farnesyl transferase.

<u>Summary of the Invention</u>

The invention provides compounds that have cyclin dependent kinase inhibiting or modulating activity and glycogen synthase kinase-3 (GSK3) inhibiting or modulating activity, and which it is envisaged will be useful in preventing or treating disease states or conditions mediated by the kinases.

Accordingly, in one aspect, the invention provides the use of a compound of the formula (I) as defined herein for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by a cyclin dependent kinase or glycogen synthase kinase-3.

In another aspect, the invention provides a method for the prophylaxis or treatment of a disease state or condition mediated by a cyclin dependent kinase or glycogen synthase kinase-3, which method comprises administering to a subject in need thereof a compound of the formula (I) as defined herein.

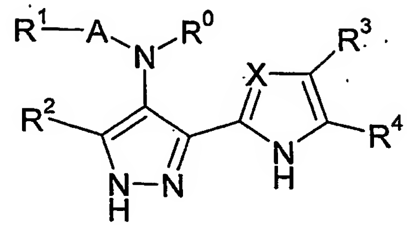
This invention also provides a method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, which method comprises administering to the mammal a compound of the formula (I) as defined herein in an amount effective in inhibiting abnormal cell growth.

This invention further provides a method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, the method comprising administering to the mammal a compound of the formula (I) as defined herein in an amount effective to inhibit cdk2 or glycogen synthase kinase-3 activity.

In another aspect, the invention provides a method of inhibiting a cyclin dependent kinase or glycogen synthase kinase-3, which method comprises contacting the kinase with a kinase-inhibiting compound of the formula (I) as defined herein.

The invention further provides a method of modulating a cellular process (for example cell division) by inhibiting the activity of a cyclin dependent kinase or glycogen synthase kinase-3 using a compound of the formula (I) as defined herein.

The compounds of the invention are represented by the general formula (I):



wherein

X is CR^5 or N;

A is a bond or $-(CH_2)_m-(B)_n-$;

B is C=O, $NR^g(C=O)$ or O(C=O) wherein R^g is hydrogen or C_{1-4} hydrocarbyl optionally substituted by hydroxy or C_{1-4} alkoxy;

m is 0, 1 or 2;

n is 0 or 1;

R^0 is hydrogen or, together with NR^g when present, forms a group $-(CH_2)_p-$ wherein p is 2 to 4;

R^1 is hydrogen, a carbocyclic or heterocyclic group having from 3 to 12 ring members, or an optionally substituted C_{1-8} hydrocarbyl group;

R^2 is hydrogen, halogen, methoxy, or a C_{1-4} hydrocarbyl group optionally substituted by halogen, hydroxyl or methoxy;

R^3 and R^4 together with the carbon atoms to which they are attached form an optionally substituted fused carbocyclic or heterocyclic ring having from 5 to 7 ring members of which up to 3 can be heteroatoms selected from N, O and S; and

R^5 is hydrogen, a group R^2 or a group R^{10} wherein R^{10} is selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members; a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^c, SO_2NR^c or NR^cSO_2; and R^b is selected from hydrogen, carbocyclic and heterocyclic groups having from 3 to 12 ring members, and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group

may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

R^c is selected from hydrogen and C_{1-4} hydrocarbyl; and

X^1 is O, S or NR^c and X^2 is =O, =S or =NR^c.

General Preferences and Definitions

The following general preferences and definitions shall apply to each of the moieties R^1 to R^6 and any sub-definition, sub-group or embodiment thereof, unless the context indicates otherwise.

References to "carbocyclic" and "heterocyclic" groups as used herein, either in the context of R^1 to R^6 and sub-definitions thereof or otherwise shall, unless the context indicates otherwise, include both aromatic and non-aromatic ring systems. Thus, for example, the term "carbocyclic and heterocyclic groups having from 3 to 12 ring members" includes within its scope aromatic, non-aromatic, unsaturated, partially saturated and fully saturated carbocyclic and heterocyclic ring systems.

The carbocyclic or heterocyclic groups can be aryl or heteroaryl groups having from 5 to 12 ring members, more usually from 5 to 10 ring members. The term "aryl" as used herein refers to a carbocyclic group having aromatic character and the term "heteroaryl" is used herein to denote a heterocyclic group having aromatic character. The terms "aryl" and "heteroaryl" embrace polycyclic (e.g. bicyclic) ring systems wherein one or more rings are non-aromatic, provided that at least one ring is aromatic. In such polycyclic systems, the group may be attached by the aromatic ring, or to a non-aromatic ring. The aryl or heteroaryl groups can be monocyclic or bicyclic groups and can be unsubstituted or substituted with one or more substituents, for example one or more groups R^{10} as defined herein.

The term non-aromatic group embraces unsaturated ring systems without aromatic character, partially saturated and fully saturated carbocyclic and heterocyclic ring systems. The terms "unsaturated" and "partially saturated" refer to rings wherein the ring structure(s) contains atoms sharing more than one valence bond i.e. the ring

contains at least one multiple bond e.g. a C=C, C≡C or N=C bond. The term "fully saturated" refers to rings where there are no multiple bonds between ring atoms. Saturated carbocyclic groups include cycloalkyl groups as defined below. Partially saturated carbocyclic groups include cycloalkenyl groups as defined below, for example cyclopentenyl, cycloheptenyl and cyclooctenyl.

Examples of heteroaryl groups are monocyclic and bicyclic groups containing from five to twelve ring members, and more usually from five to ten ring members. The heteroaryl group can be, for example, a five membered or six membered monocyclic ring or a bicyclic structure formed from fused five and six membered rings or two fused six membered rings. Each ring may contain up to about four heteroatoms typically selected from nitrogen, sulphur and oxygen. Typically the heteroaryl ring will contain up to 3 heteroatoms, more usually up to 2, for example a single heteroatom. In one embodiment, the heteroaryl ring contains at least one ring nitrogen atom. The nitrogen atoms in the heteroaryl rings can be basic, as in the case of an imidazole or pyridine, or essentially non-basic as in the case of an indole or pyrrole nitrogen. In general the number of basic nitrogen atoms present in the heteroaryl group, including any amino group substituents of the ring, will be less than five.

Examples of heteroaryl groups include but are not limited to pyridine, pyrrole, furan, thiophene, imidazole, oxazole, oxadiazole, oxatriazole, isoxazole, thiazole, isothiazole, pyrazole, pyrazine, pyridazine, pyrimidine, triazine, triazole, tetrazole, quinoline, isoquinoline, benzfuran, benzthiophene, chroman, thiochroman, benzimidazole, benzoxazole, benzisoxazole, benzthiazole, benzisothiazole, isobenzofuran, indole, isoindole, indolizine, indoline, isoindoline, purine (e.g., adenine, guanine), indazole, benzodioxole, chromene, isochromene, chroman, isochroman, benzodioxan, quinolizine, benzoxazine, benzodiazine, pyridopyridine, pyrazolopyridine, quinoxaline, quinazoline, cinnoline, phthalazine, naphthyridine and pteridine groups.

Examples of polycyclic aryl and heteroaryl groups containing an aromatic ring and a non-aromatic ring include tetrahydronaphthalene, tetrahydroisoquinoline, tetrahydroquinoline, dihydrobenzthiene, dihydrobenzfuran, 2,3-dihydro-benzo[1,4]dioxine, benzo[1,3]dioxole, 4,5,6,7-tetrahydrobenzofuran, indoline and indane groups.

Examples of carbocyclic aryl groups include phenyl, naphthyl, indenyl, and tetrahydronaphthyl groups.

Examples of non-aromatic heterocyclic groups are groups having from 3 to 12 ring members, more usually 5 to 10 ring members. Such groups can be monocyclic or bicyclic, for example, and typically have from 1 to 5 heteroatom ring members (more usually 1, 2, 3 or 4 heteroatom ring members), usually selected from nitrogen, oxygen and sulphur. The heterocylic groups can contain, for example, cyclic ether moieties (e.g as in tetrahydrofuran and dioxane), cyclic thioether moieties (e.g. as in tetrahydrothiophene and dithiane), cyclic amine moieties (e.g. as in pyrrolidine), cyclic sulphones (e.g. as in sulfolane and sulfolene)), cyclic sulphoxides, cyclic sulphonamides and combinations thereof (e.g. thiomorpholine).

Particular examples include morpholine, piperidine (e.g. 1-piperidinyl, 2-piperidinyl 3-piperidinyl and 4-piperidinyl), pyrrolidine (e.g. 1-pyrrolidinyl, 2-pyrrolidinyl and 3-pyrrolidinyl), pyrrolidone, pyran (2H-pyran or 4H-pyran), dihydrothiophene, dihydropyran, dihydrofuran, dihydrothiazole, tetrahydrofuran, tetrahydrothiophene, dioxane, tetrahydropyran (e.g. 4-tetrahydro pyranyl), imidazoline, imidazolidinone, oxazoline, thiazoline, 2-pyrazoline, pyrazolidine, piperazine, and N-alkyl piperazines such as N-methyl piperazine. In general, preferred non-aromatic heterocyclic groups include morpholine, and N-alkyl piperazines.

Examples of non-aromatic carbocyclic groups include cycloalkane groups such as cyclohexyl and cyclopentyl, cycloalkenyl groups such as cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl, as well as cyclohexadienyl, cyclooctatetraene, tetrahydronaphthenyl and decalinyl.

Where reference is made herein to carbocyclic and heterocyclic groups, the carbocyclic or heterocyclic ring can, unless the context indicates otherwise, be unsubstituted or substituted by one or more substituent groups R^{10} selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members; a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^c, SO_2NR^c or NR^cSO_2; and R^b is selected from hydrogen, carbocyclic and heterocyclic groups having from 3 to 12 ring members, and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$; or two adjacent groups R^{10}, together with the carbon atoms or heteroatoms to which they are attached may form a 5-membered heteroaryl ring or a 5- or 6-membered non-aromatic heterocyclic ring, wherein the said heteroaryl and heterocyclic groups contain up to 3 heteroatom ring members selected from N, O and S;

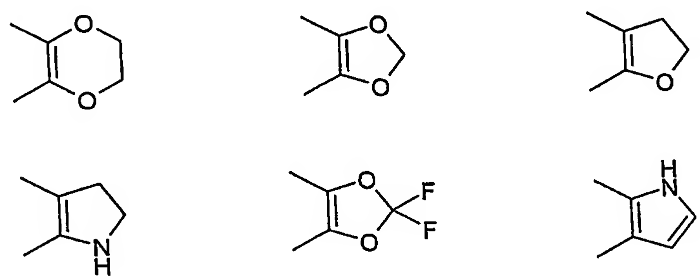
R^c is selected from hydrogen and C_{1-4} hydrocarbyl; and

X^1 is O, S or NR^c and X^2 is =O, =S or =NR^c.

Where the substituent group R^{10} comprises or includes a carbocyclic or heterocyclic group, the said carbocyclic or heterocyclic group may be unsubstituted or may itself be substituted with one or more further substituent groups R^{10}. In one sub-group of compounds of the formula (I), such further substituent groups R^{10} may include carbocyclic or heterocyclic groups, which are typically not themselves further substituted. In another sub-group of compounds of the formula (I), the said further substituents do not include carbocyclic or heterocyclic groups but are otherwise selected from the groups listed above in the definition of R^{10}.

Where the carbocyclic and heterocyclic groups have a pair of substituents on adjacent ring atoms, the two substituents may be linked so as to form a cyclic group. For example, an adjacent pair of substituents on adjacent carbon atoms of a

ring may be linked via one or more heteroatoms and optionally substituted alkylene groups to form a fused oxa-, dioxa-, aza-, diaza- or oxa-aza-cycloalkyl group. Examples of such linked substituent groups include:



Examples of halogen substituents include fluorine, chlorine, bromine and iodine. Fluorine and chlorine are particularly preferred.

In the definition of the compounds of the formula (I) above and as used hereinafter, the term "hydrocarbyl" is a generic term encompassing aliphatic, alicyclic and aromatic groups having an all-carbon backbone, except where otherwise stated. In certain cases, as defined herein, one or more of the carbon atoms making up the carbon backbone may be replaced by a specified atom or group of atoms. Examples of such groups include alkyl, cycloalkyl, cycloalkenyl, carbocyclic aryl, alkenyl, alkynyl, cycloalkylalkyl, cycloalkenylalkyl, and carbocyclic aralkyl, aralkenyl and aralkynyl groups. Such groups can be unsubstituted or substituted by one or more substituents as defined herein. The examples and preferences expressed below apply to each of the hydrocarbyl substituent groups or hydrocarbyl-containing substituent groups referred to in the various definitions of substituents for compounds of the formula (I) unless the context indicates otherwise.

Generally by way of example, the hydrocarbyl groups can have up to eight carbon atoms, unless the context requires otherwise. Within the sub-set of hydrocarbyl groups having 1 to 8 carbon atoms, particular examples are C_{1-6} hydrocarbyl groups, such as C_{1-4} hydrocarbyl groups (e.g. C_{1-3} hydrocarbyl groups or C_{1-2}

hydrocarbyl groups), specific examples being any individual value or combination of values selected from C_1, C_2, C_3, C_4, C_5, C_6, C_7 and C_8 hydrocarbyl groups.

The term "alkyl" covers both straight chain and branched chain alkyl groups. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 2-pentyl, 3-pentyl, 2-methyl butyl, 3-methyl butyl, and n-hexyl and its isomers. Within the sub-set of alkyl groups having 1 to 8 carbon atoms, particular examples are C_{1-6} alkyl groups, such as C_{1-4} alkyl groups (e.g. C_{1-3} alkyl groups or C_{1-2} alkyl groups).

Examples of cycloalkyl groups are those derived from cyclopropane, cyclobutane, cyclopentane, cyclohexane and cycloheptane. Within the sub-set of cycloalkyl groups the cycloalkyl group will have from 3 to 8 carbon atoms, particular examples being C_{3-6} cycloalkyl groups.

Examples of alkenyl groups include, but are not limited to, ethenyl (vinyl), 1-propenyl, 2-propenyl (allyl), isopropenyl, butenyl, buta-1,4-dienyl, pentenyl, and hexenyl. Within the sub-set of alkenyl groups the alkenyl group will have 2 to 8 carbon atoms, particular examples being C_{2-6} alkenyl groups, such as C_{2-4} alkenyl groups.

Examples of cycloalkenyl groups include, but are not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl and cyclohexenyl. Within the sub-set of cycloalkenyl groups the cycloalkenyl groups have from 3 to 8 carbon atoms, and particular examples are C_{3-6} cycloalkenyl groups.

Examples of alkynyl groups include, but are not limited to, ethynyl and 2-propynyl (propargyl) groups. Within the sub-set of alkynyl groups having 2 to 8 carbon atoms, particular examples are C_{2-6} alkynyl groups, such as C_{2-4} alkynyl groups.

Examples of carbocyclic aryl groups include substituted and unsubstituted phenyl groups.

Examples of cycloalkylalkyl, cycloalkenylalkyl, carbocyclic aralkyl, aralkenyl and aralkynyl groups include phenethyl, benzyl, styryl, phenylethynyl, cyclohexylmethyl, cyclopentylmethyl, cyclobutylmethyl, cyclopropylmethyl and cyclopentenylmethyl groups.

When present, a hydrocarbyl group can be optionally substituted by one or more substituents selected from hydroxy, oxo, alkoxy, carboxy, halogen, cyano, nitro, amino, mono- or di-C_{1-4} hydrocarbylamino, and monocyclic or bicyclic carbocyclic and heterocyclic groups having from 3 to 12 (typically 3 to 10 and more usually 5 to 10) ring members. Preferred substituents include halogen such as fluorine. Thus, for example, the substituted hydrocarbyl group can be a partially fluorinated or perfluorinated group such as difluoromethyl or trifluoromethyl. In one embodiment preferred substituents include monocyclic carbocyclic and heterocyclic groups having 3-7 ring members.

One or more carbon atoms of a hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$ wherein X^1 and X^2 are as hereinbefore defined. For example, 1, 2, 3 or 4 carbon atoms of the hydrocarbyl group may be replaced by one of the atoms or groups listed, and the replacing atoms or groups may be the same or different. Examples of groups in which a carbon atom of the hydrocarbyl group has been replaced by a replacement atom or group as defined above include ethers and thioethers (C replaced by O or S), amides, esters, thioamides and thioesters (C replaced by $X^1C(X^2)$ or $C(X^2)X^1$), sulphones and sulphoxides (C replaced by SO or SO_2) and amines (C replaced by NR^c).

Where an amino group has two hydrocarbyl substituents, they may, together with the nitrogen atom to which they are attached, and optionally with another heteroatom such as nitrogen, sulphur, or oxygen, link to form a ring structure of 4 to 7 ring members.

The definition "R^a-R^b" as used herein, either with regard to substituents present on a carbocyclic or heterocyclic moiety, or with regard to other substituents present at

other locations on the compounds of the formula (I), includes *inter alia* compounds wherein R^a is selected from a bond, O, CO, OC(O), SC(O), $NR^cC(O)$, OC(S), SC(S), $NR^cC(S)$, $OC(NR^c)$, $SC(NR^c)$, $NR^cC(NR^c)$, C(O)O, C(O)S, $C(O)NR^c$, C(S)O, C(S)S, C(S) NR^c, $C(NR^c)O$, $C(NR^c)S$, $C(NR^c)NR^c$, OC(O)O, SC(O)O, $NR^cC(O)O$, OC(S)O, SC(S)O, $NR^cC(S)O$, $OC(NR^c)O$, $SC(NR^c)O$, $NR^cC(NR^c)O$, OC(O)S, SC(O)S, $NR^cC(O)S$, OC(S)S, SC(S)S, $NR^cC(S)S$, $OC(NR^c)S$, $SC(NR^c)S$, $NR^cC(NR^c)S$, $OC(O)NR^c$, $SC(O)NR^c$, $NR^cC(O)$ NR^c, $OC(S)NR^c$, SC(S) NR^c, $NR^cC(S)NR^c$, $OC(NR^c)NR^c$, $SC(NR^c)NR^c$, $NR^cC(NR^cNR^c$, S, SO, SO_2, NR^c, SO_2NR^c and NR^cSO_2 wherein R^c is as hereinbefore defined.

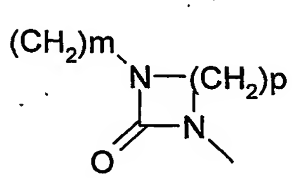
The moiety R^b can be hydrogen or it can be a group selected from carbocyclic and heterocyclic groups having from 3 to 12 ring members (typically 3 to 10 and more usually from 5 to 10), and a C_{1-8} hydrocarbyl group optionally substituted as hereinbefore defined. Examples of hydrocarbyl, carbocyclic and heterocyclic groups are as set out above.

<u>Specific Embodiments of and Preferences for R^1 to R^5 and R^{10}</u>

In formula (I), X can be CR^5 or N. In one particular embodiment, X is N. In another particular embodiment, X is CH. Preferably X is N.

R^0 can be hydrogen or, together with the group R^g when present, can form a bridging group $-(CH_2)_p-$ wherein p is 2 to 4, more usually 2-3, e.g. 2. Preferably R^0 is hydrogen.

When R^0 and the group R^g form a bridging group $-(CH_2)_p-$, the entity $-(CH_2)_m-(B)_n-NR^0-$ can be represented thus:



When A is a bond or a group $-(CH_2)_m-(B)_n-$ wherein n is 0, X can be N or CR^5 wherein R^5 is hydrogen or a group R^{10}. More preferably, X is N.

When A is a bond or a group $-(CH_2)_m-(B)_n-$ wherein n is 1, it is preferred that X is N or CR^5 wherein R^5 is hydrogen or a group R^2. More preferably, X is N.

Where R^5 is other than hydrogen, more particularly when n is 1, it is preferably a small substituent containing no more than 14 atoms, for example a C_{1-4} alkyl or cycloalkyl group such as methyl, ethyl, propyl and butyl, or cyclopropyl and cyclobutyl.

A is a bond or $-(CH_2)_m-(B)_n-$ wherein B is C=O, $NR^g(C=O)$ or O(C=O), m is 0, 1 or 2; and n is 0 or 1. In one preferred group of compounds of the invention, m is 0 or 1, n is 1 and B is C=O or $NR^g(C=O)$, preferably C=O. More preferably, m is 0, n is 1 and B is C=O. It is presently preferred that when B is $NR^g(C=O)$, R^g is hydrogen.

It will be appreciated that the moiety R^1-A-NH linked to the 4-position of the pyrazole ring can take the form of an amine $R^1-(CH_2)_m$-NH, an amide $R^1-(CH_2)_m$-C(=O)NH, a urea $R^1-(CH_2)_m$-NHC(=O)NH or a carbamate $R^1-(CH_2)_m$-OC(=O)NH wherein in each case m is 0, 1 or 2, preferably 0 or 1 and most preferably 0.

R^1 is hydrogen, a carbocyclic or heterocyclic group having from 3 to 12 ring members, or an optionally substituted C_{1-8} hydrocarbyl group as hereinbefore defined. Examples of carbocyclic and heterocyclic, and optionally substituted hydrocarbyl groups are as set out above.

Particular examples of R^1 include heteroaryl groups selected from pyrazolo[1,5-a]pyridinyl (e.g. pyrazolo[1,5-a]pyridin-3-yl), furanyl (e.g. 2-furanyl and 3-furanyl), indolyl (e.g. 3-indolyl, 4-indolyl and 7-indolyl), oxazolyl, thiazolyl (e.g. thiazol-2-yl and thiazol-5-yl), isoxazolyl (e.g. isoxazol-3-yl and isoxazol-4-yl), pyrrolyl (e.g. 3-pyrrolyl), pyridyl (e.g. 2-pyridyl), quinolinyl (e.g. quinolin-8-yl), 2,3-dihydro-benzo[1,4]dioxine (e.g. 2,3-dihydro-benzo[1,4]dioxin-5-yl), benzo[1,3]dioxole (e.g. benzo[1,3]dioxol-4-yl), 2,3-dihydrobenzofuranyl (e.g. 2,3-dihydrobenzofuran-7-yl), imidazolyl and thiophenyl (e.g. 3-thiophenyl).

Preferred R^1 heteroaryl groups include pyrazolo[1,5-a]pyridinyl, furanyl, 2,3-dihydrobenzofuranyl, thiophenyl, indolyl, thiazolyl, isoxazolyl and 2,3-dihydro-benzo[1,4]dioxine groups.

Preferred aryl groups R^1 are those based on a phenyl ring.

Preferred non-aromatic groups R^1 include monocyclic cycloalkyl and azacycloalkyl groups such as cyclohexyl, cyclopentyl and piperidinyl, particularly cyclohexyl and 4-piperidinyl groups.

Preferred substituted and unsubstituted C_{1-8} hydrocarbyl groups include trifluoromethyl and tertiary butyl groups.

Particularly preferred R^1 groups include phenyl, pyrazolo[1,5-a]pyridinyl and 2,3-dihydro-benzo[1,4]dioxine groups.

The group R^1 can be an unsubstituted or substituted carbocyclic or heterocyclic group in which one or more substituents can be selected from the group R^{10} as hereinbefore defined. In one embodiment, the substituents on R^1 may be selected from the group R^{10a} consisting of halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, heterocyclic groups having 5 or 6 ring members and up to 2 heteroatoms selected from O, N and S, a group R^a-R^b wherein R^a is a bond, O, CO, $X^3C(X^4)$, $C(X^4)X^3$, $X^3C(X^4)X^3$, S, SO, or SO_2, and R^b is selected from hydrogen, heterocyclic groups having 5 or 6 ring members and up to 2 heteroatoms selected from O, N and S, and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having 5 or 6 ring members and up to 2 heteroatoms selected from O, N and S; wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, $X^3C(X^4)$, $C(X^4)X^3$ or $X^3C(X^4)X^3$; X^3 is O or S; and X^4 is =O or =S.

In a further embodiment, the substituents on R^1 may be selected from the group R^{10b} consisting of halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, a group R^a-R^b wherein R^a is a bond, O, CO, $X^3C(X^4)$, $C(X^4)X^3$, $X^3C(X^4)X^3$, S, SO, or SO_2,

and R^b is selected from hydrogen and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy; wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, $X^3C(X^4)$, $C(X^4)X^3$ or $X^3C(X^4)X^3$; X^3 is O or S; and X^4 is =O or =S.

In another embodiment, the substituents on R^1 may be selected from halogen, hydroxy, trifluoromethyl, a group R^a-R^b wherein R^a is a bond or O, and R^b is selected from hydrogen and a C_{1-4} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxyl and halogen.

Particular examples of substituents that may be present on a group R^1 (e.g. an aryl or heteroaryl group R^1) include fluorine, chlorine, methoxy, methyl, oxazolyl, morpholino, trifluoromethyl, bromomethyl, chloroethyl, pyrrolidino, pyrrolidinylethoxy, pyrrolidinylmethyl, difluoromethoxy and morpholinomethyl.

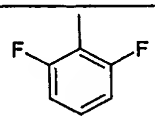
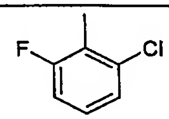
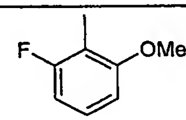
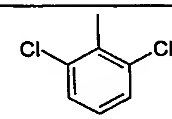
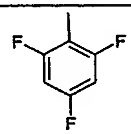
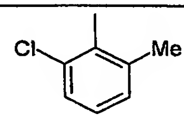
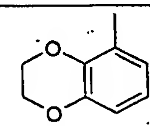
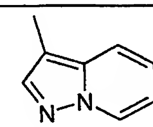
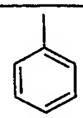
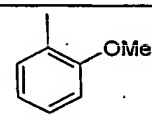
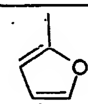
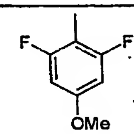
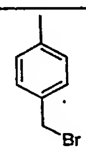
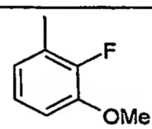
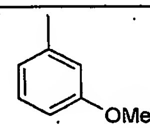
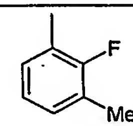
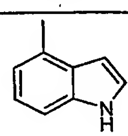
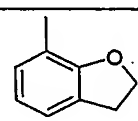
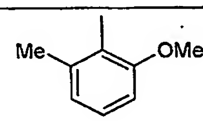
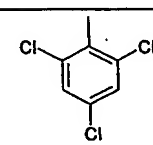
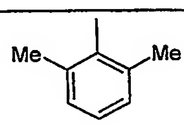
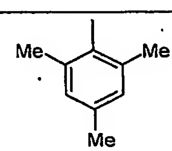
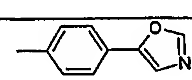
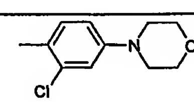
The moiety R^1 may be substituted by more than one substituent. Thus, for example, there may be 1 or 2 or 3 or 4 substituents, more typically 1, 2 or 3 substituents. In one embodiment, where R^1 is a six membered ring (e.g. a carbocyclic ring such as a phenyl ring), there may be a single substituent which may be located at any one of the 2-, 3- and 4-positions on the ring. In another embodiment, there may be two or three substituents and these may be located at the 2-, 3-, 4- or 6-positions around the ring. By way of example, a phenyl group R^1 may be 2,6-disubstituted, 2,3-disubstituted, 2,4-disubstituted 2,5-disubstituted, 2,3,6-trisubstituted or 2,4,6-trisubstituted. More particularly, a phenyl group R^1 may be disubstituted at positions 2- and 6- with substituents selected from fluorine, chlorine and R^a-R^b, where R^a is O and R^b is C_{1-4} alkyl, with fluorine being a particular substituent.

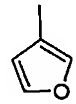
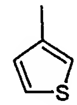
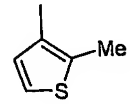
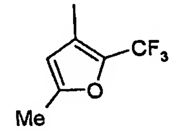
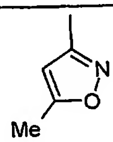
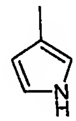
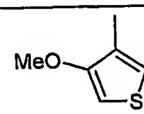
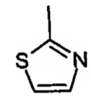
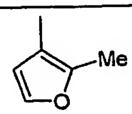
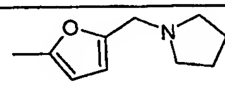
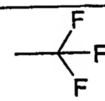
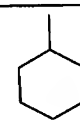
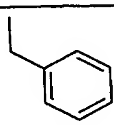
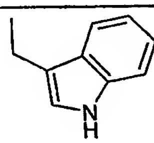
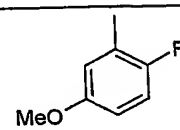
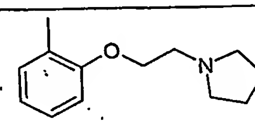
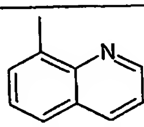
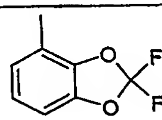
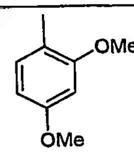
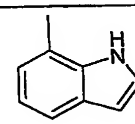
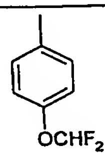
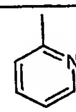
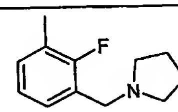
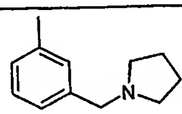
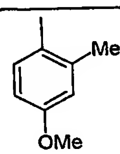
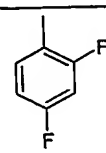
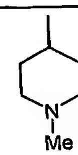
In one subgroup of compounds, the group R^1 is a five membered heteroaryl group containing 1 or 2 ring heteroatoms selected from O, N and S. Particular heteroaryl groups include furan, thiophene, pyrrole, oxazole, isoxazole and thiazole groups. The heteroaryl groups may be unsubstituted or substituted by one or more substituent groups as hereinbefore defined.

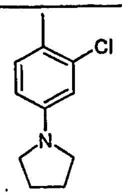
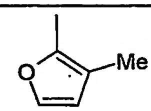
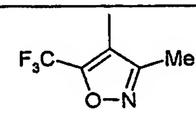
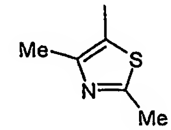
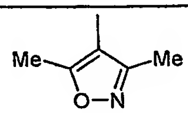
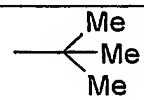
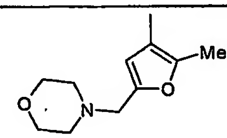
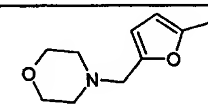
In another sub-group of compounds, R^1 is a pyrazolopyridine group, for example, a pyrazolo[1,5-a]pyridine group, such as a 3-pyrazolo[1,5-a]pyridinyl group.

Particular examples of groups R^1 include the groups A1 to A60 set out in Table 1 below.

Table 1

 A1	 A2	 A3	 A4
 A5	 A6	 A7	 A8
 A9	 A10	 A11	 A12
 A13	 A14	 A15	 A16
 A17	 A18	 A19	 A20
 A21	 A22	 A23	 A24

 A25	 A26	 A27	 A28
 A29	 A30	 A31	 A32
 A33	 A34	 A35	 A36
 A37	 A38	 A39	 A40
 A41	 A42	 A43	 A44
 A45	 A46	 A47	 A48
 A49	 A50	 A51	 A52

 A53	 A54	 A55	 A56
 A57	 A58	 A59	 A60

Preferred groups R^1 include groups A1 to A34.

Particularly preferred groups R^1 include 2,6-difluorophenyl, 2-chloro-6-fluorophenyl, 2-fluoro-6-methoxyphenyl, 2,6-dichlorophenyl, 2,4,6-trifluorophenyl, 2-chloro-6-methyl, 2,3-dihydro-benzo[1,4]dioxin-5-yl and pyrazolo[1,5-a]pyridin-3-yl.

A currently most preferred group R^1 is 2,6-difluorophenyl.

R^2 is hydrogen, halogen, methoxy, or a C_{1-4} hydrocarbyl group optionally substituted by halogen, hydroxyl or methoxy. Preferably R^2 is hydrogen, chlorine or methyl, and most preferably R^2 is hydrogen.

In the compounds of the formula (I), R^3 and R^4, together with the carbon atoms to which they are attached, form a fused heterocyclic or carbocyclic group having from 5 to 7 ring members, of which up to 3 can be heteroatoms selected from N, O and S. The fused carbocyclic or heterocyclic ring can be optionally substituted by 0 to 4 groups R^{10} as defined herein. The fused heterocyclic or carbocyclic group can be aromatic or non-aromatic but preferably is aromatic.

In one preferred group of compounds, R^3 and R^4 together with the carbon atoms to which they are attached form a fused carbocyclic group having from 5 to 7 ring members.

Fused five and six membered carbocyclic or heterocyclic groups are particularly preferred. Examples of fused heterocyclic rings include five and six membered rings such as thiazolo, isothiazolo, oxazolo, isoxazolo, pyrrolo, pyrido, thieno, furano, pyrimido, pyrazolo, pyrazino, and imidazolo fused rings. It is preferred that the fused heterocyclic group is selected from six membered ring groups, one particularly preferred group being the pyrido group.

Examples of fused carbocyclic rings include five and six membered rings such as benzo, dihydro or tetrahydro-benzo and cyclopenta- fused rings. Six membered rings are preferred. One particularly preferred group is the benzo group.

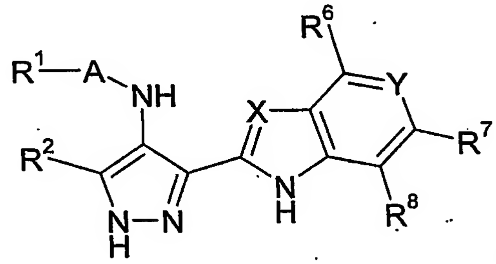
The fused carbocyclic or heterocyclic group can be optionally substituted by one or more groups R^{10} as hereinbefore defined.

In one embodiment, the substituents on the fused carbocyclic or heterocyclic group may be selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, monocyclic carbocyclic and heterocyclic groups having from 3 to 7 (typically 5 or 6) ring members, a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^c, SO_2NR^c or NR^cSO_2; and R^b is selected from hydrogen, a carbocyclic or heterocyclic group with 3-7 ring members and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, a carbocyclic or heterocyclic group with 3-7 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$; and R^c, X^1 and X^2 are as hereinbefore defined, or two adjacent groups R^{10} together with the carbon atoms or heteroatoms to which they are attached may form a 5-membered heteroaryl ring or a 5- or 6-membered non-aromatic heterocyclic ring, wherein the said heteroaryl and heterocyclic groups contain up to 3 heteroatom ring members selected from N, O and S.

Preferred R^{10} groups on the fused carbocyclic or heterocyclic group formed by R^3 and R^4 include halogen, a group R^a-R^b wherein R^a is a bond, O, CO, $C(X^2)X^1$, and

R^b is selected from hydrogen, heterocyclic group having 3-7 ring members and a C_{1-4} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, heterocyclic group with 3-7 ring members.

One preferred group of compounds of the invention is represented by the formula (II):



(II)

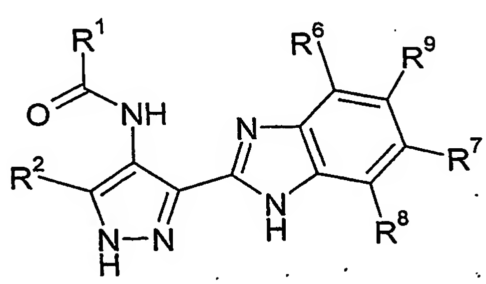
wherein R^1, R^2 and X are as hereinbefore defined;
Y is N or CR^9 wherein R^9 is hydrogen or a group R^{10}; and
R^6, R^7 and R^8 are the same or different and each is hydrogen or a group R^{10} as hereinbefore defined.

In one sub-group of compounds of the formula (II), X is N.

In another sub-group of compounds of the formula (II), Y is CR^9.

When Y is N, it is preferred that R^6 is other than amino.

In one embodiment, the compounds of the invention are represented by the formula (III):



(III)

wherein R^1, R^2 and R^6 to R^9 are as hereinbefore defined.

Within formula (III), it is preferred that R^2 is hydrogen or C_{1-4} alkyl, and more typically R^2 is hydrogen.

Within the group of compounds defined by the formula (III), R^1 is preferably 2,3 disubstituted, 2,6 disubstituted or 2,4,6, trisubstituted phenyl or 2, 3-dihydro-benzo[1,4]dioxine, where the substituents are selected from halogen and C_{1-4} alkoxy.

More preferably R^1 is selected from 2,6-difluorophenyl, 2-fluoro-6-methoxyphenyl, 2-chloro-6-fluorophenyl, 2,6-dichlorophenyl, 2,4,6-trifluorophenyl, 2,6-difluoro-4-methoxyphenyl, and 2,3-dihydro-benzo[1,4]dioxine.

One particularly preferred group R^1 is 2,6-difluorophenyl.

The moieties R^6, R^7, R^8 and R^9 are typically selected from hydrogen, halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, monocyclic carbocyclic and heterocyclic groups having from 3 to 12 (preferably 3 to 7, and more typically 5 or 6) ring members, a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^c, SO_2NR^c or NR^cSO_2; and R^b is selected from hydrogen, a carbocyclic or heterocyclic group with 3-7 ring members and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, C_{1-4} acyloxy, oxo, halogen, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, a carbocyclic or heterocyclic group with 3-7 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$; and R^c, X^1 and X^2; or an adjacent pair of substituents selected from R^6, R^7, R^8 and R^9 together with the carbon atoms to which they are attached may form a non-aromatic five or six membered ring containing up to three heteroatoms selected from O, N and S.

In one embodiment, R^6 to R^9 are each hydrogen or are selected from halogen, cyano, hydroxy, trifluoromethyl, nitro, a group R^a-R^b wherein R^a is a bond, O, CO or $C(X^2)X^1$ and R^b is selected from hydrogen, heterocyclic groups having from 3 to

12 ring members (preferably 4 to 7 ring members), and a C_{1-8} hydrocarbyl group (preferably a C_{1-4} hydrocarbyl group), optionally substituted by one or more substituents selected from hydroxy, C_{1-4} acyloxy, mono- or di-C_{1-4} hydrocarbylamino, heterocyclic groups having from 3 to 12 ring members, more preferably 4 to 7 ring members; where R^c is selected from hydrogen and C_{1-4} hydrocarbyl, X^1 is O or NR^c and X^2 is =O.

In another embodiment, R^6, R^7, R^8 and R^9 are selected from hydrogen, fluorine, chlorine, bromine, nitro, trifluoromethyl, carboxy, a group R^a-R^b wherein R^a is a bond, O, CO, $C(X^2)X^1$, and R^b is selected from hydrogen, heterocyclic groups having 3-7 ring members (e.g. pyrrolidine, N-methyl piperazine or morpholine) and a C_{1-4} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, carboxy, C_{1-4} acyloxy, amino, mono- or di-C_{1-4} hydrocarbylamino, heterocyclic groups with 3-7 ring members (e.g. pyrrolidine, N-methyl piperazine or morpholine); or an adjacent pair of substituents selected from R^6, R^7, R^8 and R^9 together with the carbon atoms to which they are attached may form a non-aromatic five or six membered ring containing one or two oxygen atoms as ring members.

In a more preferred embodiment, R^6, R^7, R^8 and R^9 are selected from hydrogen, fluorine, chlorine, trifluoromethyl, a group R^a-R^b wherein R^a is a bond, O, CO, $C(X^2)X^1$, and R^b is selected from hydrogen, saturated heterocyclic groups having 5-6 ring members and a C_{1-2} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, carboxy, C_{1-2} acyloxy, amino, mono- or di-C_{1-4} hydrocarbylamino, heterocyclic groups with 5-6 ring members; or an adjacent pair of substituents selected from R^6, R^7, R^8 and R^9 may form a methylenedioxy or ethylenedioxy group each optionally substituted by one or more fluorine atoms.

In another embodiment, particular substituent groups R^6 to R^9 include halogen, nitro, carboxy, a group R^a-R^b wherein R^a is a bond, O, CO, $C(X^2)X^1$, and R^b is selected from hydrogen, heterocyclic group having 3-7 ring members and a C_{1-4} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, heterocyclic group with 3-7 ring members.

Whereas each of R^6 to R^9 can be hydrogen or a substituent as hereinbefore defined, it is preferred that at least one, more preferably at least two, of R^6 to R^9 are hydrogen.

In one particular embodiment, one of R^6 to R^9 is a substituent and the others each are hydrogen. For example, R^6 can be a substituent group and R^7 to R^9 can each be hydrogen, or R^9 can be a substituent and R^6, R^7 and R^8 can each be hydrogen.

In another particular embodiment, two of R^6 to R^9 are substituents and the other two are both hydrogen. For example, R^6 and R^9 can both be substituents when R^7 and R^8 are both hydrogen; or R^6 and R^7 can both be substituents when R^8 and R^9 are both hydrogen; or R^7 and R^9 can both be substituents when R^6 and R^8 are both hydrogen.

R^6 is preferably selected from:
hydrogen;
halogen (preferably fluorine or chlorine);
methyl optionally substituted by a substituent selected from hydroxy, halogen (e.g. fluorine, preferably difluoro or trifluoro, and more preferably trifluoro) and $NR^{11}R^{12}$; and
$C(=O)NR^{11}R^{12}$;
wherein R^{11} and R^{12} are the same or different and each is selected from hydrogen and C_{1-4} alkyl or R^{11} and R^{12} together with the nitrogen atom form a five or six membered heterocyclic ring having 1 or 2 heteroatom ring members selected from O, N and S (preferably O and N).

R^7 is preferably selected from:
hydrogen;
halogen (preferably fluorine or chlorine);
C_{1-4} alkoxy (for example methoxy);
methyl optionally substituted by a substituent selected from hydroxy, halogen (e.g. fluorine, preferably difluoro or trifluoro, and more preferably trifluoro) and $NR^{11}R^{12}$; and

$C(=O)NR^{11}R^{12}$;

wherein R^{11} and R^{12} are the same or different and each is selected from hydrogen and C_{1-4} alkyl or R^{11} and R^{12} together with the nitrogen atom form a five or six membered heterocyclic ring having 1 or 2 heteroatom ring members selected from O, N and S (preferably O and N).

R^8 is preferably selected from hydrogen, fluorine and methyl, most preferably hydrogen.

R^9 is preferably selected from:

hydrogen;

halogen (preferably fluorine or chlorine);

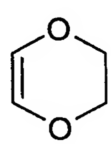
C_{1-4} alkoxy (for example methoxy);

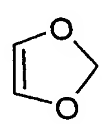
methyl optionally substituted by a substituent selected from hydroxy, halogen (e.g. fluorine, preferably difluoro or trifluoro, and more preferably trifluoro) and $NR^{11}R^{12}$; and

$C(=O)NR^{11}R^{12}$;

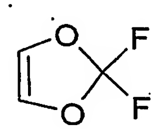
wherein R^{11} and R^{12} are the same or different and each is selected from hydrogen and C_{1-4} alkyl or R^{11} and R^{12} together with the nitrogen atom form a five or six membered heterocyclic ring having 1 or 2 heteroatom ring members selected from O, N and S (preferably O and N).

Alternatively, R^6 and R^9, or R^7 and R^9, together with the carbon atoms to which they are attached may form a cyclic group selected from:





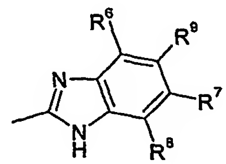
and



In the foregoing definitions, when R^{11} and R^{12} together with the nitrogen atom in the group $NR^{11}R^{12}$ form a five or six membered heterocyclic ring, the heteroatom ring members are preferably selected from O and N. The heterocyclic ring is typically non-aromatic and examples of such rings include morpholine, piperazine, N-C_{1-4}-

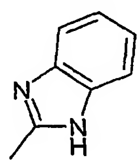
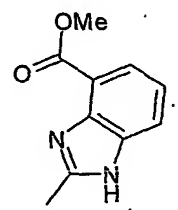
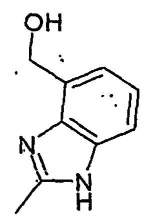
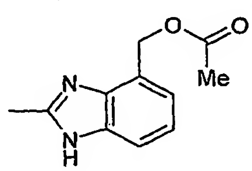
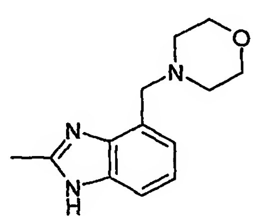
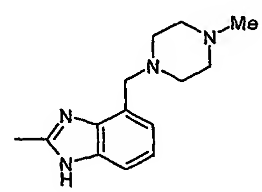
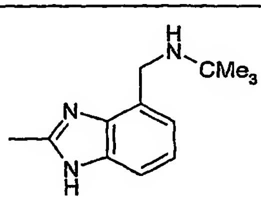
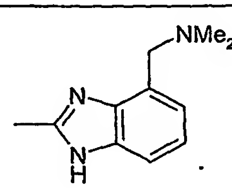
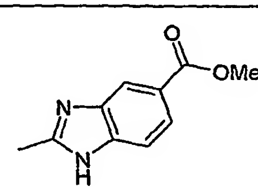
alkylpiperazine, piperidine and pyrrolidine. Particular examples of N-C_{1-4}-alkylpiperazine groups include N-methylpiperazine and N-isopropylpiperazine.

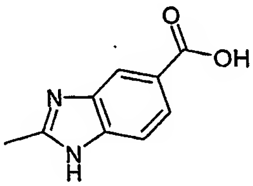
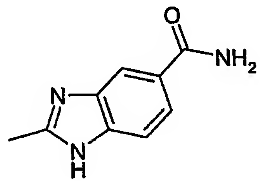
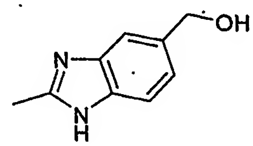
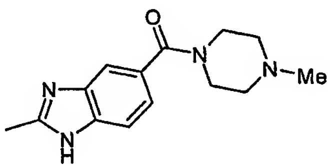
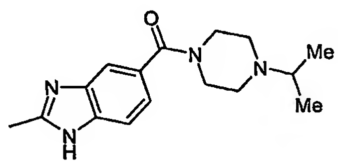
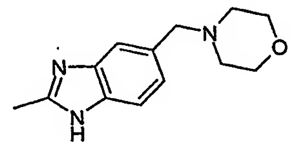
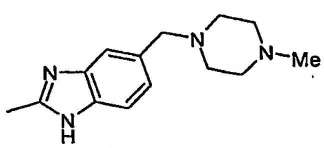
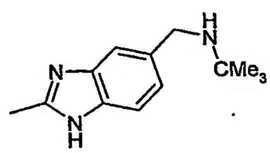
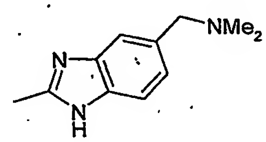
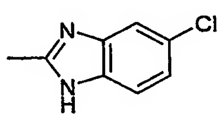
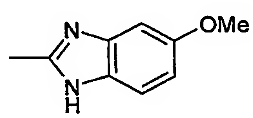
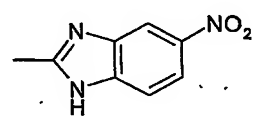
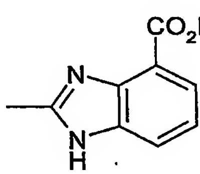
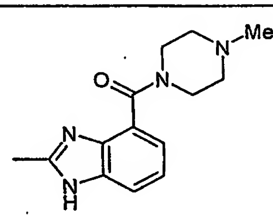
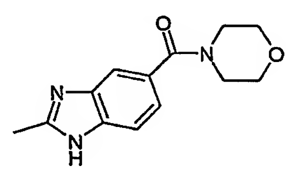
Preferred groups R^6 to R^9 include those in which the benzimidazole group

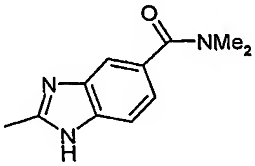
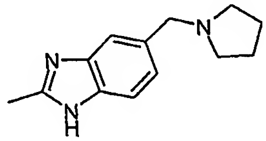
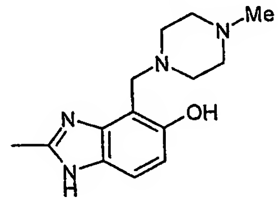
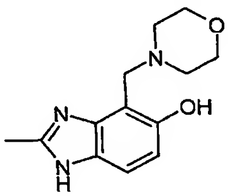
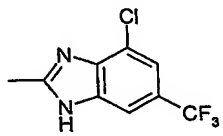
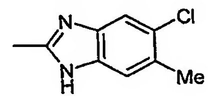
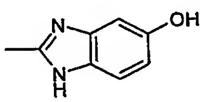
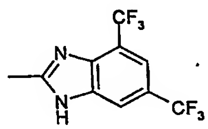
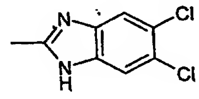
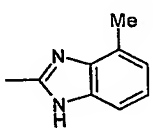
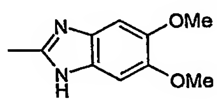
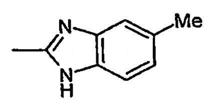
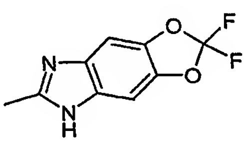
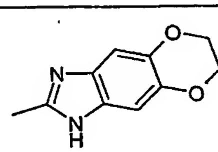
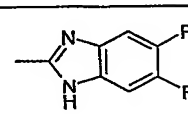


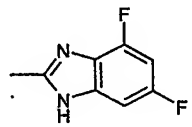
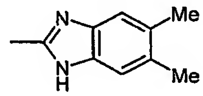
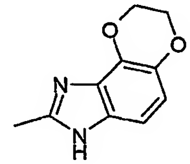
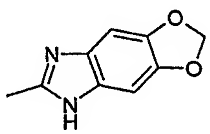
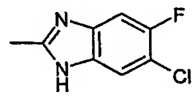
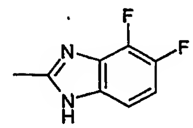
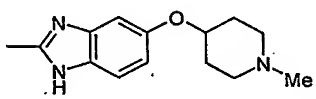
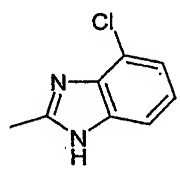
is as shown in Table 2 below.

Table 2

 B1	 B2	 B3
 B4	 B5	 B6
 B7	 B8	 B9

 B10	 B11	 B12
 B13	 B14	 B15
 B16	 B17	 B18
 B19	 B20	 B21
 B22	 B23	 B24

 B25	 B26	 B27
 B28	 B29	 B30
 B31	 B32	 B33
 B34	 B35	 B36
 B37	 B38	 B39

 B40	 B41	 B42
 B43	 B44	 B45
 B46	 B47	

Of the benzimidazole groups set out in Table 2 above, particular groups include groups B1, B3, B5-B8, B11-B20, B23-B30 and B32-B47.

Particularly preferred groups are groups B1, B3, B5-B8, B11-B20, B24, B25, B27-B30 and B32-B47.

For the avoidance of doubt, it is to be understood that each general and specific preference, embodiment and example of the groups R^1 may be combined with each general and specific preference, embodiment and example of the groups R^2 and/or R^3 and that all such combinations are embraced by this application.

For example, any one of the groups R^1 (e.g. as in R^1-A where A is C=O) shown in Table 1 may be combined with any one of the benzimidazole groups shown in Table 2.

The various functional groups and substituents making up the compounds of the formula (I) are typically chosen such that the molecular weight of the compound of the formula (I) does not exceed 1000. More usually, the molecular weight of the compound will be less than 750, for example less than 700, or less than 650, or less than 600, or less than 550. More preferably, the molecular weight is less than 525 and, for example, is 500 or less.

Particular compounds of the invention are as illustrated in the examples below.

Many compounds of the formula (I) can exist in the form of salts, for example acid addition salts or, in certain cases salts of organic and inorganic bases such as carboxylate, sulphonate and phosphate salts. All such salts are within the scope of this invention, and references to compounds of the formula (I) include the salt forms of the compounds.

Acid addition salts may be formed with a wide variety of acids, both inorganic and organic. Examples of acid addition salts include salts formed with hydrochloric, hydriodic, phosphoric, nitric, sulphuric, citric, lactic, succinic, maleic, malic, isethionic, fumaric, benzenesulphonic, toluenesulphonic, methanesulphonic, ethanesulphonic, naphthalenesulphonic, valeric, acetic, propanoic, butanoic, malonic, glucuronic and lactobionic acids.

For example, if the compound is anionic, or has a functional group which may be anionic (e.g., -COOH may be -COO$^-$), then a salt may be formed with a suitable cation. Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as Na^+ and K^+, alkaline earth cations such as Ca^{2+} and Mg^{2+}, and other cations such as Al^{3+}. Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e., NH_4^+) and substituted ammonium ions (e.g., NH_3R^+, $NH_2R_2^+$, NHR_3^+, NR_4^+). Examples of some suitable substituted ammonium ions are those derived from: ethylamine, diethylamine, dicyclohexylamine, triethylamine, butylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine, choline, meglumine, and

tromethamine, as well as amino acids, such as lysine and arginine. An example of a common quaternary ammonium ion is $N(CH_3)_4^+$.

Where the compounds of the formula (I) contain an amine function, these may form quaternary ammonium salts, for example by reaction with an alkylating agent according to methods well known to the skilled person. Such quaternary ammonium compounds are within the scope of formula (I).

Compounds of the formula (I) containing an amine function may also form N-oxides. A reference herein to a compound of the formula (I) that contains an amine function also includes the N-oxide.

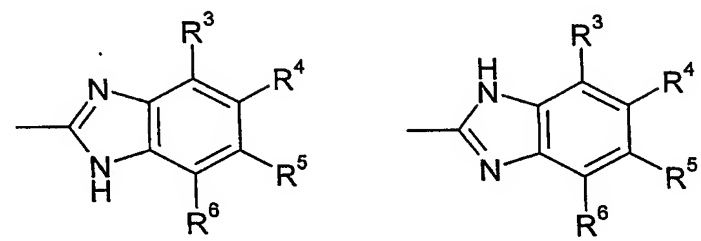
Where a compound contains several amine functions, one or more than one nitrogen atom may be oxidised to form an N-oxide. Particular examples of N-oxides are the N-oxides of a tertiary amine or a nitrogen atom of a nitrogen-containing heterocycle.

N-Oxides can be formed by treatment of the corresponding amine with an oxidizing agent such as hydrogen peroxide or a per-acid (e.g. a peroxycarboxylic acid), see for example *Advanced Organic Chemistry*, by Jerry March, 4th Edition, Wiley Interscience, pages. More particularly, N-oxides can be made by the procedure of L. W. Deady (*Syn. Comm.* 1977, 7, 509-514) in which the amine compound is reacted with *m*-chloroperoxybenzoic acid (MCPBA), for example, in an inert solvent such as dichloromethane.

Compounds of the formula may exist in a number of different geometric isomeric, and tautomeric forms and references to compounds of the formula (I) include all such forms. For the avoidance of doubt, where a compound can exist in one of several geometric isomeric or tautomeric forms and only one is specifically described or shown, all others are nevertheless embraced by formula (I).

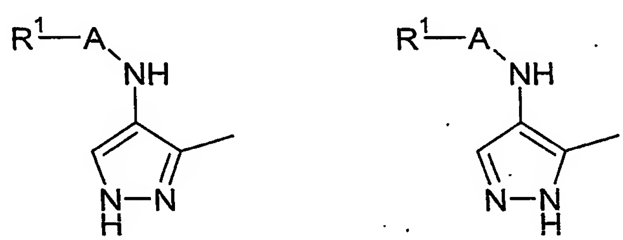
For example, in compounds of the formula (I) the benzimidazole group may take either of the following two tautomeric forms A and B. For simplicity, the general

formula (I) illustrates form A but the formula is to be taken as embracing both tautomeric forms.



A B

The pyrazole ring may also exhibit tautomerism and can exist in the two tautomeric forms C and D below.



C D

Esters such as carboxylic acid esters and acyloxy esters of the compounds of formula (I) bearing a carboxylic acid group or a hydroxyl group are also embraced by Formula (I). Examples of esters are compounds containing the group -C(=O)OR, wherein R is an ester substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Particular examples of ester groups include, but are not limited to, $-C(=O)OCH_3$, $-C(=O)OCH_2CH_3$, $-C(=O)OC(CH_3)_3$, and -C(=O)OPh. Examples of acyloxy (reverse ester) groups are represented by -OC(=O)R, wherein R is an acyloxy substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Particular examples of acyloxy groups include, but are not limited to, $-OC(=O)CH_3$ (acetoxy), $-OC(=O)CH_2CH_3$, $-OC(=O)C(CH_3)_3$, -OC(=O)Ph, and $-OC(=O)CH_2Ph$.

Also encompassed by formula (I) are any polymorphic forms of the compounds, solvates (e.g. hydrates), complexes (e.g. inclusion complexes or clathrates with compounds such as cyclodextrins, or complexes with metals) of the compounds, and pro-drugs of the compounds. By "prodrugs" is meant for example any compound that is converted *in vivo* into a biologically active compound of the formula (I).

For example, some prodrugs are esters of the active compound (e.g., a physiologically acceptable metabolically labile ester). During metabolism, the ester group (-C(=O)OR) is cleaved to yield the active drug. Such esters may be formed by esterification, for example, of any of the carboxylic acid groups (-C(=O)OH) in the parent compound, with, where appropriate, prior protection of any other reactive groups present in the parent compound, followed by deprotection if required.

Examples of such metabolically labile esters include those of the formula -C(=O)OR wherein R is:
C_{1-7}alkyl
(e.g., -Me, -Et, -nPr, -iPr, -nBu, -sBu, -iBu, -tBu);
C_{1-7}aminoalkyl
(e.g., aminoethyl; 2-(N,N-diethylamino)ethyl; 2-(4-morpholino)ethyl); and
acyloxy-C_{1-7}alkyl
(e.g., acyloxymethyl;
acyloxyethyl;
pivaloyloxymethyl;
acetoxymethyl;
1-acetoxyethyl;
1-(1-methoxy-1-methyl)ethyl-carbonxyloxyethyl;
1-(benzoyloxy)ethyl; isopropoxy-carbonyloxymethyl;
1-isopropoxy-carbonyloxyethyl; cyclohexyl-carbonyloxymethyl;
1-cyclohexyl-carbonyloxyethyl;
cyclohexyloxy-carbonyloxymethyl;
1-cyclohexyloxy-carbonyloxyethyl;

(4-tetrahydropyranyloxy) carbonyloxymethyl;
1-(4-tetrahydropyranyloxy)carbonyloxyethyl;
(4-tetrahydropyranyl)carbonyloxymethyl; and
1-(4-tetrahydropyranyl)carbonyloxyethyl).

Also, some prodrugs are activated enzymatically to yield the active compound, or a compound which, upon further chemical reaction, yields the active compound (for example, as in ADEPT, GDEPT, LIDEPT, etc.). For example, the prodrug may be a sugar derivative or other glycoside conjugate, or may be an amino acid ester derivative.

Where the compounds of the formula (I) contain chiral centres, all individual optical forms such as enantiomers, epimers and diastereoisomers, as well as racemic mixtures of the compounds are within the scope of formula (I).

The compounds of the formula (I) are inhibitors of cyclin dependent kinases. For example, compounds of the invention have activity against CDK1, CDK2, CDK3, CDK5, CDK6 and CDK7 kinases.

Compounds of the invention also have activity against glycogen synthase kinase-3 (GSK-3).

As a consequence of their activity in modulating or inhibiting CDK kinases and glycogen synthase kinase, they are expected to be useful in providing a means of arresting, or recovering control of, the cell cycle in abnormally dividing cells. It is therefore anticipated that the compounds will prove useful in treating or preventing proliferative disorders such as cancers. It is also envisaged that the compounds of the invention will be useful in treating conditions such as viral infections, autoimmune diseases and neurodegenerative diseases for example.

CDKs play a role in the regulation of the cell cycle, apoptosis, transcription, differentiation and CNS function. Therefore, CDK inhibitors could be useful in the treatment of diseases in which there is a disorder of proliferation, apoptosis or

differentiation such as cancer. In particular RB+ve tumours may be particularly sensitive to CDK inhibitors.

Examples of cancers which may be inhibited include, but are not limited to, a carcinoma, for example a carcinoma of the bladder, breast, colon (e.g. colorectal carcinomas such as colon adenocarcinoma and colon adenoma), kidney, epidermal, liver, lung, for example adenocarcinoma, small cell lung cancer and non-small cell lung carcinomas, oesophagus, gall bladder, ovary, pancreas e.g. exocrine pancreatic carcinoma, stomach, cervix, thyroid, prostate, or skin, for example squamous cell carcinoma; a hematopoietic tumour of lymphoid lineage, for example leukemia, acute lymphocytic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma, or Burkett's lymphoma; a hematopoietic tumor of myeloid lineage, for example acute and chronic myelogenous leukemias, myelodysplastic syndrome, or promyelocytic leukemia; thyroid follicular cancer; a tumour of mesenchymal origin, for example fibrosarcoma or habdomyosarcoma, ; a tumor of the central or peripheral nervous system, for example astrocytoma, neuroblastoma, glioma or schwannoma; melanoma; seminoma; teratocarcinoma; osteosarcoma; xenoderoma pigmentoum; keratoctanthoma; thyroid follicular cancer; or Kaposi's sarcoma.

CDKs are also known to play a role in apoptosis, proliferation, differentiation and transcription and therefore CDK inhibitors could also be useful in the treatment of the following diseases other than cancer; viral infections, for example herpes virus, pox virus, Epstein-Barr virus, Sindbis virus, adenovirus, HIV, HPV, HCV and HCMV; prevention of AIDS development in HIV-infected individuals; chronic inflammatory diseases, for example systemic lupus erythematosus, autoimmune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel disease, and autoimmune diabetes mellitus; cardiovascular diseases for example cardiac hypertrophy, restenosis, atherosclerosis; neurodegenerative disorders, for example Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotropic lateral sclerosis, retinitis pigmentosa, spinal muscular atropy and cerebellar degeneration; glomerulonephritis; myelodysplastic syndromes, ischemic

injury associated myocardial infarctions, stroke and reperfusion injury, arrhythmia, atherosclerosis, toxin-induced or alcohol related liver diseases, haematological diseases, for example, chronic anemia and aplastic anemia; degenerative diseases of the musculoskeletal system, for example, osteoporosis and arthritis, aspirin-senstive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases and cancer pain.

It has also been discovered that some cyclin-dependent kinase inhibitors can be used in combination with other anticancer agents. For example, the cytotoxic activity of cyclin-dependent kinase inhibitor flavopiridol, has been used with other anticancer agents in combination therapy.

Thus, in the pharmaceutical compositions, uses or methods of this invention for treating a disease or condition comprising abnormal cell growth, the disease or condition comprising abnormal cell growth in one embodiment is a cancer.

Particular subsets of cancers include breast cancer, ovarian cancer, colon cancer, prostate cancer, oesophageal cancer, squamous cancer and non-small cell lung carcinomas.

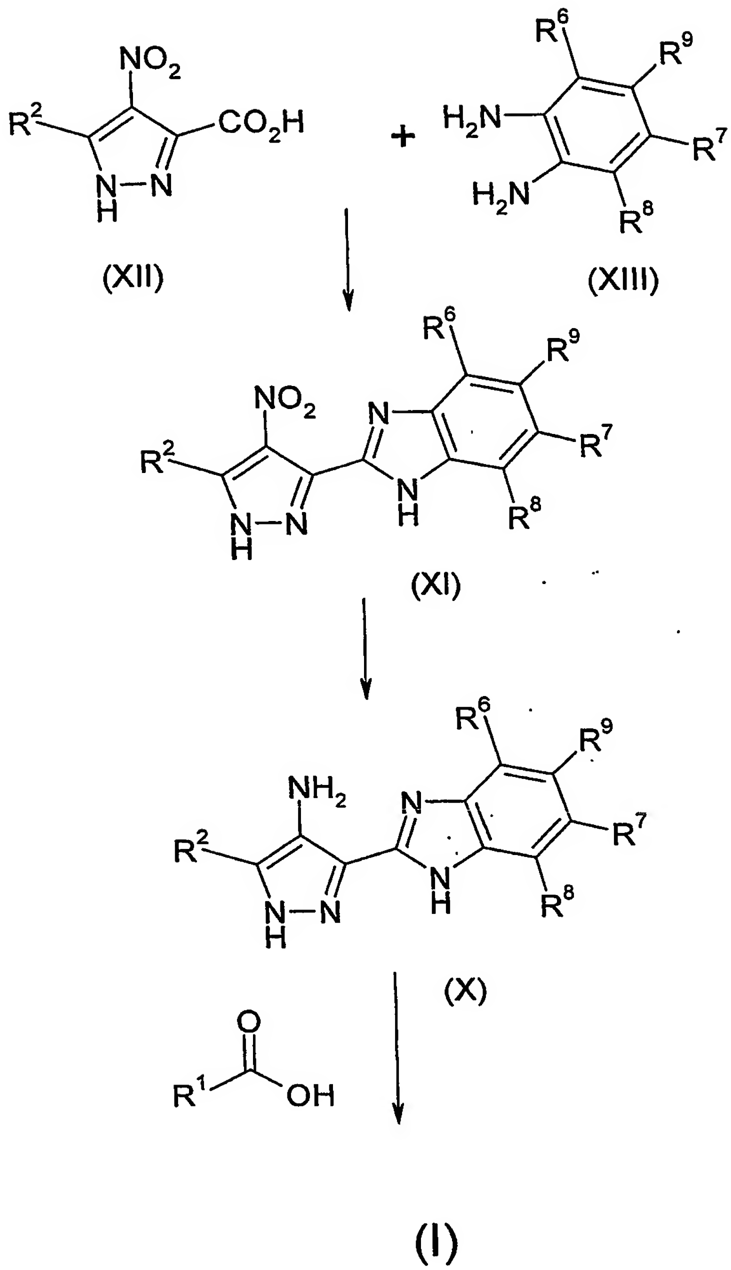
The activity of the compounds of the invention as inhibitors of cyclin dependent kinases and glycogen synthase kinase-3 can be measured using the assays set forth in the examples below and the level of activity exhibited by a given compound can be defined in terms of the IC_{50} value. Preferred compounds of the present invention are compounds having an IC_{50} value of less than 1 micromole, more preferably less than 0.1 micromole.

<u>Methods for the Preparation of Compounds of the Formula (I)</u>

Compounds of the formula (I) can be prepared in accordance with synthetic methods well known to the skilled person.

Compounds of the formula (I) wherein R^1-A- forms an acyl group can be prepared as illustrated in Scheme 1 below.

As shown in Scheme 1, an amine of the formula (X) can be reacted with with a carboxylic acid, or reactive derivative thereof, of the formula R^1-B-CO_2H under standard amide formation conditions. Thus, for example, the coupling reaction between the carboxylic acid and the amine (X) can be carried out in the presence of a reagent of the type commonly used in the formation of peptide linkages. Examples of such reagents include 1,3-dicyclohexylcarbodiimide (DCC) (Sheehan *et al*, *J. Amer. Chem Soc.* 1955, 77, 1067), 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide (EDC) (Sheehan *et al, J. Org. Chem., 1961, 26, 2525*), uronium-based coupling agents such as *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) (L. A. Carpino, *J. Amer. Chem. Soc.*, 1993, 115, 4397) and phosphonium-based coupling agents such as 1-benzo-triazolyloxytris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP) (Castro *et al, Tetrahedron Letters*, 1990, 31, 205). Carbodiimide-based couling agents are advantageously used in combination with1-hydroxybenzotriazole (HOBt) (Konig *et al*, *Chem. Ber.*, 103, 708, 2024-2034). Preferred coupling reagents include EDC and DCC in combination with HOBt.



Scheme 1 (X)

The coupling reaction is typically carried out in a non-aqueous, non-protic solvent such as acetonitrile, dioxan, dimethylsulphoxide, dichloromethane, dimethylformamide or N-methylpyrrolidine, or in an aqueous solvent optionally

together with one or more miscible co-solvents. The reaction can be carried out at room temperature or, where the reactants are less reactive (for example in the case of electron-poor anilines bearing electron withdrawing groups such as sulphonamide groups) at an appropriately elevated temperature. The reaction may be carried out in the presence of a non-interfering base, for example a tertiary amine such as triethylamine or *N,N*-diisopropylethylamine.

As an alternative, a reactive derivative of the carboxylic acid, e.g. an anhydride or acid chloride, may be used. Reaction with a reactive derivative such an anhydride is typically accomplished by stirring the amine and anhydride at room temperature in the presence of a base such as pyridine.

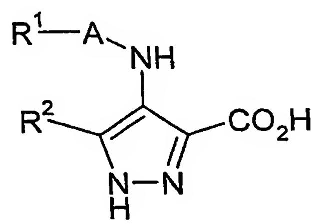
Amines of the formula (X) can be prepared by reduction of the corresponding nitro-compound of the formula (XI) under standard conditions. The reduction may be effected, for example by catalytic hydrogenation in the presence of a catalyst such as palladium on carbon in a polar solvent such as ethanol or dimethylformamide at room temperature.

When X is nitrogen, the compounds of the formula (XI) can be prepared by reaction of a nitro-pyrazole carboxylic acid of the formula (XII) with a diamine of the formula (XII). The reaction between the diamine (XIII) and carboxylic acid (XII) can be carried out in the presence of a reagent such as DCC or EDC in the presence of HOBt as described above, under amide coupling conditions as described previously, to give an intermediate *ortho*-aminophenylamide (not shown) which is then cyclised to form the benzimidazole ring. The final cyclisation step is typically carried out by heating under reflux in the presence of acetic acid.

Diamines of the formula (XIII) can be obtained commercially or can be prepared from appropriately substituted phenyl precursor compounds using standard chemistry and well known functional group interconversions, see for example, *Fiesers' Reagents for Organic Synthesis*, Volumes 1-17, John Wiley, edited by Mary Fieser (ISBN: 0-471-58283-2), and *Organic Syntheses*, Volumes 1-8, John Wiley, edited by Jeremiah P. Freeman (ISBN: 0-471-31192-8),

1995. Examples of methods of preparing diamines of the formula (XIII) are provided in the examples below.

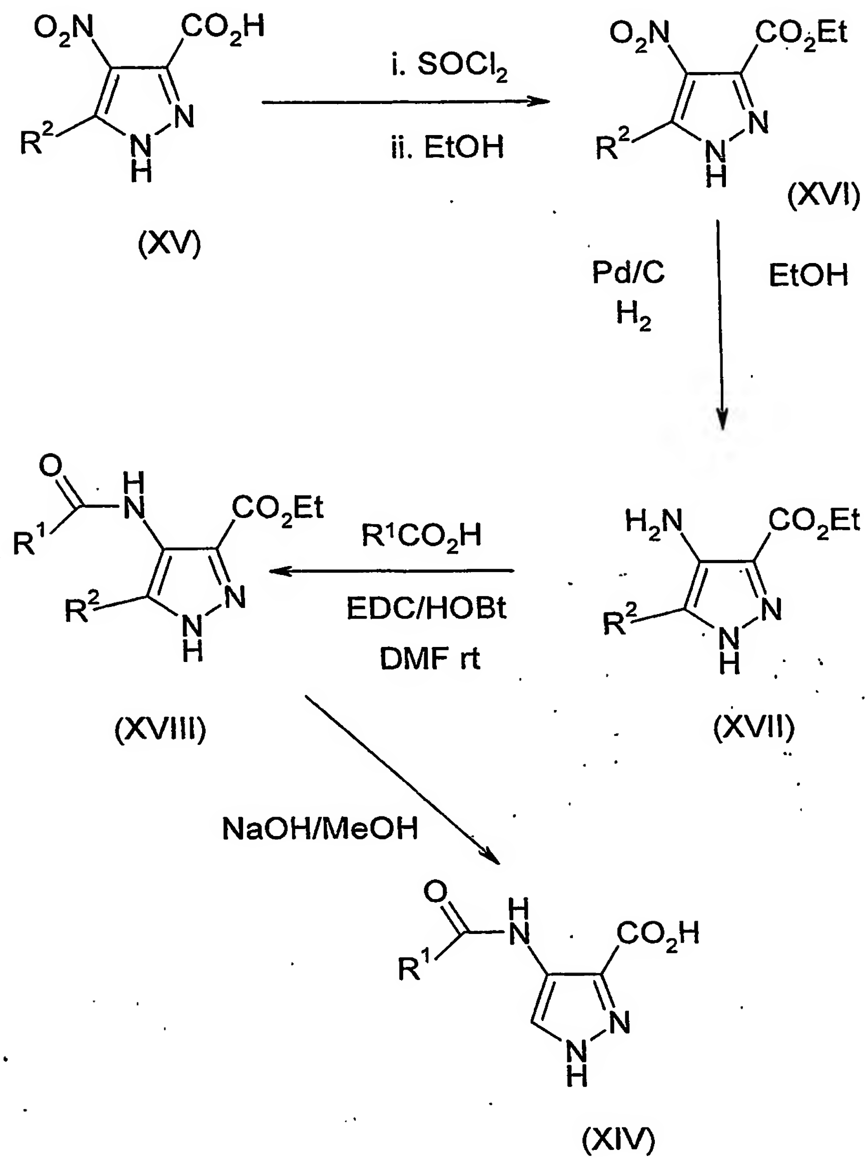
The diamines of the formula (XIII) can also be reacted with carboxylic acids of the formula (XIV) to give compounds of the formula (I).



(XIV)

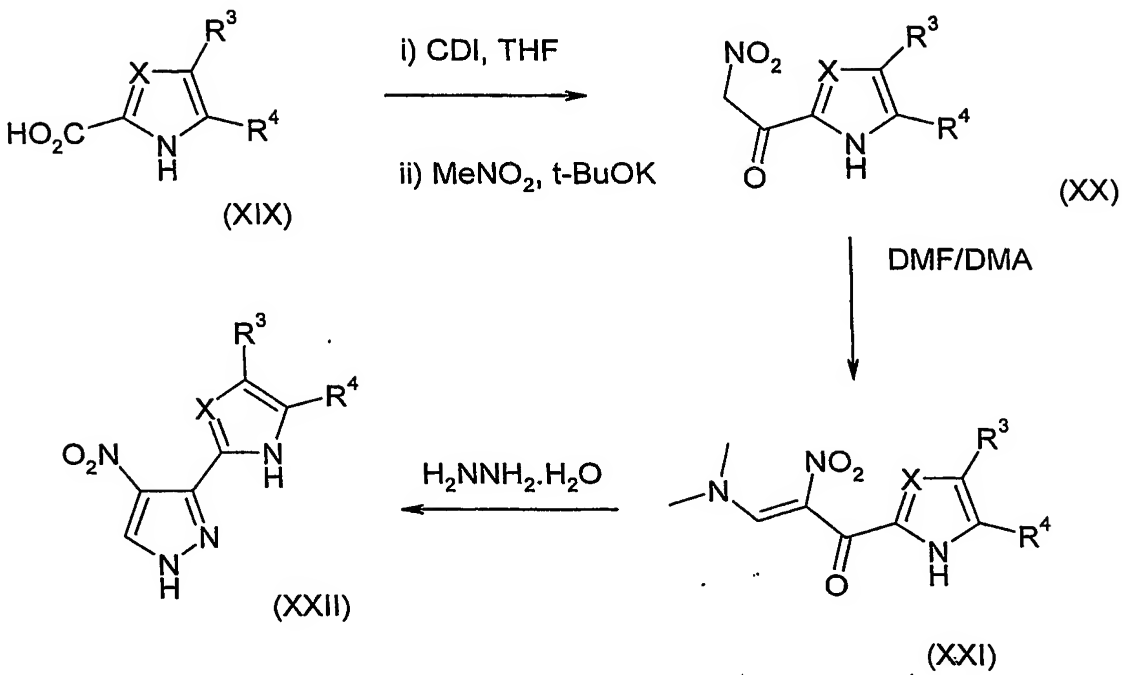
The reaction of the diamine (XIII) with the carboxylic acid (XIV) can be carried out under conditions analogous to those described above for preparing the nitro-compounds (XI). Carboxylic acids of the formula (XIV) can be prepared by the sequence of reactions shown in Scheme 2.

As shown in Scheme 2, a substituted or unsubstituted 4-nitro-3-pyrazole carboxylic acid (XV) can be esterified by reaction with thionyl chloride to give the acid chloride intermediate followed by reaction with ethanol to form the ethyl ester (XVI). Alternatively, the esterification can be carried out by reacting the alcohol and carboxylic acid in the presence of an acidic catalyst, one example of which is thionyl chloride. The reaction is typically carried out at room temperature using the esterifying alcohol (e.g. ethanol) as the solvent. The nitro group can then be reduced using palladium on carbon according to standard methods to give the amine (XVII). The amine (XVII) is coupled with an appropriate carboxylic acid R^1-CO_2H under amide forming conditions the same as or analogous to those described above to give the amide (XVIII). The ester group of the amide (XVIII) can then be hydrolysed using an alkali metal hydroxide such as sodium hydroxide in a polar water miscible solvent such as methanol, typically at room temperature.



Scheme 2

A further synthetic route to compounds of the formula (I) is shown in Scheme 3 below.



Scheme 3

As illustrated in scheme 3, a carboxylic acid of the formula (XIX) can be activated with 1,1'-carbonyl diimidazole in an appropriate aprotic solvent. Subsequent reaction with the anion of nitromethane gives a 2-nitroketone (XX) (Rudolph et al, *Org. Lett.*, 2001, 3(20), 3153-3155). Further reaction of a 2-nitroketone with dimethylformamide-dimethylacetal at elevated temperature gives an α,β-unsaturated ketone (XXI) (Jachak et al, *Montash. Chem.*, 1993,124(2), 199-207), which upon heating with hydrazine hydrate gives a pyrazole of formula (XXII).

The procedure illustrated in Scheme 3 is of particular utility in the preparation of compounds when X is a group CR^5.

Compounds of the formula (I) I which A is NH(CO) can be prepared using standard methods for the synthesis of ureas. For example, such compounds can be prepared by reacting an aminopyrazole compound of the formula (X) with a suitably

substituted phenylisocyanate in a polar solvent such as DMF. The reaction is conveniently carried out at room temperature.

In many of the reactions described above, it may be necessary to protect one or more groups to prevent reaction from taking place at an undesirable location on the molecule. Examples of protecting groups, and methods of protecting and deprotecting functional groups, can be found in *Protective Groups in Organic Synthesis* (T. Green and P. Wuts; 3rd Edition; John Wiley and Sons, 1999). A hydroxy group may be protected, for example, as an ether (-OR) or an ester (-OC(=O)R), for example, as: a t-butyl ether; a benzyl, benzhydryl (diphenylmethyl), or trityl (triphenylmethyl) ether; a trimethylsilyl or t-butyldimethylsilyl ether; or an acetyl ester ($-OC(=O)CH_3$, -OAc). An aldehyde or ketone group may be protected, for example, as an acetal ($R-CH(OR)_2$) or ketal ($R_2C(OR)_2$), respectively, in which the carbonyl group (>C=O) is converted to a diether ($>C(OR)_2$), by reaction with, for example, a primary alcohol. The aldehyde or ketone group is readily regenerated by hydrolysis using a large excess of water in the presence of acid. An amine group may be protected, for example, as an amide (-NRCO-R) or a urethane (-NRCO-OR), for example, as: a methyl amide ($-NHCO-CH_3$); a benzyloxy amide ($-NHCO-OCH_2C_6H_5$, -NH-Cbz); as a t-butoxy amide ($-NHCO-OC(CH_3)_3$, -NH-Boc); a 2-biphenyl-2-propoxy amide ($-NHCO-OC(CH_3)_2C_6H_4C_6H_5$, -NH-Bpoc), as a 9-fluorenylmethoxy amide (-NH-Fmoc), as a 6-nitroveratryloxy amide (-NH-Nvoc), as a 2-trimethylsilylethyloxy amide (-NH-Teoc), as a 2,2,2-trichloroethyloxy amide (-NH-Troc), as an allyloxy amide (-NH-Alloc), or as a 2(-phenylsulphonyl)ethyloxy amide (-NH-Psec). Other protecting groups for amines, such as cyclic amines and heterocyclic N-H groups, include toluenesulfonyl (tosyl) and methanesulfonyl (mesyl) groups and benzyl groups such as a *para*-methoxybenzyl (PMB) group. A carboxylic acid group may be protected as an ester for example, as: an C_{1-7} alkyl ester (e.g., a methyl ester; a t-butyl ester); a C_{1-7} haloalkyl ester (e.g., a C_{1-7} trihaloalkyl ester); a triC_{1-7} alkylsilyl-C_{1-7}alkyl ester; or a C_{5-20} aryl-C_{1-7} alkyl ester (e.g., a benzyl ester; a nitrobenzyl ester); or as an amide, for example, as a methyl amide. A thiol group may be protected, for example, as a

thioether (-SR), for example, as: a benzyl thioether; an acetamidomethyl ether (-S-$CH_2NHC(=O)CH_3$).

Pharmaceutical Formulations

The invention also provides compounds of the formula (I) as hereinbefore defined in the form of pharmaceutical compositions.

The pharmaceutical compositions can be in any form suitable for oral, parenteral, topical, intranasal, ophthalmic, otic, rectal, intra-vaginal, or transdermal administration. Where the compositions are intended for parenteral administration, they can be formulated for intravenous, intramuscular, intraperitoneal, subcutaneous administration or for direct delivery into a target organ or tissue by injection, infusion or other means of delivery.

Pharmaceutical dosage forms suitable for oral administration include tablets, capsules, caplets, pills, lozenges, syrups, solutions, powders, granules, elixirs and suspensions, sublingual tablets, wafers or patches and buccal patches.

Pharmaceutical compositions containing compounds of the formula (I) can be formulated in accordance with known techniques, see for example, Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA, USA.

Thus, tablet compositions can contain a unit dosage of active compound together with an inert diluent or carrier such as a sugar or sugar alcohol, eg; lactose, sucrose, sorbitol or mannitol; and/or a non-sugar derived diluent such as sodium carbonate, calcium phosphate, calcium carbonate, or a cellulose or derivative thereof such as methyl cellulose, ethyl cellulose, hydroxypropyl methyl cellulose, and starches such as corn starch. Tablets may also contain such standard ingredients as binding and granulating agents such as polyvinylpyrrolidone, disintegrants (e.g. swellable crosslinked polymers such as crosslinked carboxymethylcellulose), lubricating agents (e.g. stearates), preservatives (e.g. parabens), antioxidants (e.g. BHT), buffering agents (for example phosphate or citrate buffers), and effervescent agents

such as citrate/bicarbonate mixtures. Such excipients are well known and do not need to be discussed in detail here.

Capsule formulations may be of the hard gelatin or soft gelatin variety and can contain the active component in solid, semi-solid, or liquid form. Gelatin capsules can be formed from animal gelatin or synthetic or plant derived equivalents thereof.

The solid dosage forms (eg; tablets, capsules etc.) can be coated or un-coated, but typically have a coating, for example a protective film coating (e.g. a wax or varnish) or a release controlling coating. The coating (e.g. a Eudragit ™ type polymer) can be designed to release the active component at a desired location within the gastro-intestinal tract. Thus, the coating can be selected so as to degrade under certain pH conditions within the gastrointestinal tract, thereby selectively release the compound in the stomach or in the ileum or duodenum.

Instead of, or in addition to, a coating, the drug can be presented in a solid matrix comprising a release controlling agent, for example a release delaying agent which may be adapted to selectively release the compound under conditions of varying acidity or alkalinity in the gastrointestinal tract. Alternatively, the matrix material or release retarding coating can take the form of an erodible polymer (e.g. a maleic anhydride polymer) which is substantially continuously eroded as the dosage form passes through the gastrointestinal tract. As a further alternative, the active compound can be formulated in a delivery system that provides osmotic control of the release of the compound. Osmotic release and other delayed release or sustained release formulations may be prepared in accordance with methods well known to those skilled in the art.

Compositions for topical use include ointments, creams, sprays, patches, gels, liquid drops and inserts (for example intraocular inserts). Such compositions can be formulated in accordance with known methods.

Compositions for parenteral administration are typically presented as sterile aqueous or oily solutions or fine suspensions, or may be provided in finely divided

sterile powder form for making up extemporaneously with sterile water for injection.

Examples of formulations for rectal or intra-vaginal administration include pessaries and suppositories which may be, for example, formed from a shaped moldable or waxy material containing the active compound.

Compositions for administration by inhalation may take the form of inhalable powder compositions or liquid or powder sprays, and can be administrated in standard form using powder inhaler devices or aerosol dispensing devices. Such devices are well known. For administration by inhalation, the powdered formulations typically comprise the active compound together with an inert solid powdered diluent such as lactose.

The compounds of the inventions will generally be presented in unit dosage form and, as such, will typically contain sufficient compound to provide a desired level of biological activity. For example, a formulation intended for oral administration may contain from 0.1 milligrams to 2 grams of active ingredient, more usually from 10 milligrams to 1 gram, for example, 50 milligrams to 500 milligrams.

The active compound will be administered to a patient in need thereof (for example a human or animal patient) in an amount sufficient to achieve the desired therapeutic effect.

Methods of Treatment

It is envisaged that the compounds of the formula (I) will useful in the prophylaxis or treatment of a range of disease states or conditions mediated by cyclin dependent kinases. Examples of such disease states and conditions are set out above.

Compounds of the formula (I) are generally administered to a subject in need of such administration, for example a human or animal patient, preferably a human.

The compounds will typically be administered in amounts that are therapeutically or prophylactically useful and which generally are non-toxic. However, in certain

situations (for example in the case of life threatening diseases), the benefits of administering a compound of the formula (I) may outweigh the disadvantages of any toxic effects or side effects, in which case it may be considered desirable to administer compounds in amounts that are associated with a degree of toxicity.

A typical daily dose of the compound can be in the range from 100 picograms to 100 milligrams per kilogram of body weight, more typically 10 nanograms to 10 milligrams per kilogram of bodyweight although higher or lower doses may be administered where required. Ultimately, the quantity of compound administered will be commensurate with the nature of the disease or physiological condition being treated and will be at the discretion of the physician.

The compounds of the formula (I) can be administered as the sole therapeutic agent or they can be administered in combination therapy with one of more other compounds for treatment of a particular disease state, for example a neoplastic disease such as a cancer as hereinbefore defined. Examples of other therapeutic agents that may be administered together (whether concurrently or at different time intervals) with the compounds of the formula (I) include cytotoxic agents, agents that prevent cell proliferation or radiotherapy. Examples of such agents include but are not limited to topoisomerase inhibitors, alkylating agents, antimetabolites, DNA binders and microtubule inhibitors, such as cisplatin, cyclophosphamide, doxorubicin, irinotecan, fludarabine, 5FU, taxanes and mitomycin C.

Antifungal Use

In a further aspect, the invention provides the use of the compounds of the formula (I) as hereinbefore defined as antifungal agents.

The compounds of the formula (I) may be used in animal medicine (for example in the treatment of mammals such as humans), or in the treatment of plants (e.g. in agriculture and horticulture), or as general antifungal agents, for example as preservatives and disinfectants.

In one embodiment, the invention provides a compound of the formula (I) as hereinbefore defined for use in the prophylaxis or treatment of a fungal infection in a mammal such as a human.

Also provided is the use of a compound of the formula (I) for the manufacture of a medicament for use in the prophylaxis or treatment of a fungal infection in a mammal such as a human.

For example, compounds of the invention may be administered to human patients suffering from, or at risk of infection by, topical fungal infections caused by among other organisms, species of Candida, Trichophyton, Microsporum or Epidermophyton, or in mucosal infections caused by Candida albicans (e.g. thrush and vaginal candidiasis). The compounds of the invention can also be administered for the treatment or prophylaxis of systemic fungal infections caused by, for example, Candida albicans, Cryptococcus neoformans, Aspergillus flavus, Aspergillus fumigatus, Coccidiodies, Paracoccidioides, Histoplasma or Blastomyces.

In another aspect, the invention provides an antifungal composition for agricultural (including horticultural) use, comprising a compound of the formula (I) together with an agriculturally acceptable diluent or carrier.

The invention further provides a method of treating an animal (including a mammal such as a human), plant or seed having a fungal infection, which comprises treating said animal, plant or seed, or the locus of said plant or seed, with an effective amount of a compound of the formula (I).

The invention also provides a method of treating a fungal infection in a plant or seed which comprises treating the plant or seed with an antifungally effective amount of a fungicidal composition containing a compound of the formula (I) as hereinbefore defined.

Differential screening assays may be used to select for those compounds of the present invention with specificity for non-human CDK enzymes. Compounds which

act specifically on the CDK enzymes of eukaryotic pathogens can be used as anti-fungal or anti-parasitic agents. Inhibitors of the Candida CDK kinase, CKSI, can be used in the treatment of candidiasis. Antifungal agents can be used against infections of the type hereinbefore defined, or opportunistic infections that commonly occur in debilitated and immunosuppressed patients such as patients with leukemias and lymphomas, people who are receiving immunosuppressive therapy, and patients with predisposing conditions such as diabetes mellitus or AIDS, as well as for non-immunosuppressed patients.

Assays described in the art can be used to screen for agents which may be useful for inhibiting at least one fungus implicated in mycosis such as candidiasis, aspergillosis, mucormycosis, blastomycosis, geotrichosis, cryptococcosis, chromoblastomycosis, coccidiodomycosis, conidiosporosis, histoplasmosis, maduromycosis, rhinosporidosis, nocaidiosis, para-actinomycosis, penicilliosis, monoliasis, or sporotrichosis. The differential screening assays can be used to identify anti-fungal agents which may have therapeutic value in the treatment of aspergillosis by making use of the CDK genes cloned from yeast such as Aspergillus fumigatus, Aspergillus flavus, Aspergillus niger, Aspergillus nidulans, or Aspergillus terreus, or where the mycotic infection is mucon-nycosis, the CDK assay can be derived from yeast such as Rhizopus arrhizus, Rhizopus oryzae, Absidia corymbifera, Absidia ramosa, or Mucorpusillus. Sources of other CDK enzymes include the pathogen Pneumocystis carinii.

By way of example, *in vitro* evaluation of the antifungal activity of the compounds can be performed by determining the minimum inhibitory concentration (M.I.C.) which is the lowest concentration of the test compounds, in a suitable medium, at which growth of the particular microorganism fails to occur. In practice, a series of agar plates, each having the test compound incorporated at a particular concentration is inoculated with a standard culture of, for example, Candida albicans and each plate is then incubated for an appropriate period at 37 °C. The plates are then examined for the presence or absence of growth of the fungus and the appropriate M.I.C. value is noted. Alternatively, a turbidity assay in liquid

cultures can be performed and a protocol outlining an example of this assay can be found in Example 134.

The *in vivo* evaluation of the compounds can be carried out at a series of dose levels by intraperitoneal or intravenous injection or by oral administration, to mice that have been inoculated with a fungus, e.g., a strain of Candida albicans or Aspergillus flavus. The activity of the compounds can be assessed by monitoring the growth of the fungal infection in groups of treated and untreated mice (by histology or by retrieving fungi from the infection). The activity may be measured in terms of the dose level at which the compound provides 50% protection against the lethal effect of the infection (PD_{50}).

For human antifungal use, the compounds of the formula (I) can be administered alone or in admixture with a pharmaceutical carrier selected in accordance with the intended route of administration and standard pharmaceutical practice. Thus, for example, they may be administered orally, parenterally, intravenously, intramuscularly or subcutaneously by means of the formulations described above in the section headed "Pharmaceutical Formulations".

For oral and parenteral administration to human patients, the daily dosage level of the antifungal compounds of the formula (I) can be from 0.01 to 10 mg/kg (in divided doses), depending on *inter alia* the potency of the compounds when administered by either the oral or parenteral route. Tablets or capsules of the compounds may contain, for example, from 5 mg to 0.5 g of active compound for administration singly or two or more at a time as appropriate. The physician in any event will determine the actual dosage (effective amount) which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient.

Alternatively, the antifungal compounds of formula (I) can be administered in the form of a suppository or pessary, or they may be applied topically in the form of a lotion, solution, cream, ointment or dusting powder. For example, they can be incorporated into a cream consisting of an aqueous emulsion of polyethylene

glycols or liquid paraffin; or they can be incorporated, at a concentration between 1 and 10%, into an ointment consisting of a white wax or white soft paraffin base together with such stabilizers and preservatives as may be required.

In addition to the therapeutic uses described above, anti-fungal agents developed with such differential screening assays can be used, for example, as preservatives in foodstuff, feed supplement for promoting weight gain in livestock, or in disinfectant formulations for treatment of non-living matter, e.g., for decontaminating hospital equipment and rooms. In similar fashion, side by side comparison of inhibition of a mammalian CDK and an insect CDK, such as the Drosophilia CDK5 gene (Hellmich et al. (1994) FEBS Lett 356:317-21), will permit selection amongst the compounds herein of inhibitors which discriminate between the human/mammalian and insect enzymes. Accordingly, the present invention expressly contemplates the use and formulation of the compounds of the invention in insecticides, such as for use in management of insects like the fruit fly.

In yet another embodiment, certain of the subject CDK inhibitors can be selected on the basis of inhibitory specificity for plant CDK's relative to the mammalian enzyme. For example, a plant CDK can be disposed in a differential screen with one or more of the human enzymes to select those compounds of greatest selectivity for inhibiting the plant enzyme. Thus, the present invention specifically contemplates formulations of the subject CDK inhibitors for agricultural applications, such as in the form of a defoliant or the like.

For agricultural and horticultural purposes the compounds of the invention may be used in the form of a composition formulated as appropriate to the particular use and intended purpose. Thus the compounds may be applied in the form of dusting powders, or granules, seed dressings, aqueous solutions, dispersions or emulsions, dips, sprays, aerosols or smokes. Compositions may also be supplied in the form of dispersible powders, granules or grains, or concentrates for dilution prior to use. Such compositions may contain such conventional carriers, diluents or adjuvants as are known and acceptable in agriculture and horticulture and they can be manufactured in accordance with conventional procedures. The compositions may

also incorporate other active ingredients, for example, compounds having herbicidal or insecticidal activity or a further fungicide. The compounds and compositions can be applied in a number of ways, for example they can be applied directly to the plant foliage, stems, branches, seeds or roots or to the soil or other growing medium, and they may be used not only to eradicate disease, but also prophylactically to protect the plants or seeds from attack. By way of example, the compositions may contain from 0.01 to 1 wt.% of the active ingredient. For field use, likely application rates of the active ingredient may be from 50 to 5000 g/hectare.

The invention also contemplates the use of the compounds of the formula (I) in the control of wood decaying fungi and in the treatment of soil where plants grow, paddy fields for seedlings, or water for perfusion. Also contemplated by the invention is the use of the compounds of the formula (I) to protect stored grain and other non-plant loci from fungal infestation.

EXAMPLES

The invention will now be illustrated, but not limited, by reference to the specific embodiments described in the following examples.

In the examples, the compounds prepared were characterised by liquid chromatography and mass spectroscopy using the systems and operating conditions set out below. Where chlorine is present, the mass quoted for the compound is for ^{35}Cl. Several systems were used, as described below, and these were equipped with identical chromatography columns and were set up to run under closely similar operating conditions. The operating conditions used are also described below.

Platform system 1

System:	Waters 2790/Platform LC
Mass Spec Detector:	Micromass Platform LC
PDA Detector:	Waters 996 PDA

Analytical conditions:

Eluent A:	5% CH_3CN in 95% H_2O (0.1% Formic Acid)
Eluent B:	CH_3CN (0.1% Formic Acid)
Gradient:	10-95% eluent B
Flow:	1.2 ml/min
Column:	Synergi 4µm Max-RP C_{12}, 80A, 50 x 4.6 mm (Phenomenex)

MS conditions:

Capillary voltage:	3.5 kV
Cone voltage:	30 V
Source Temperature:	120 °C

FractionLynx system 1

System:	Waters FractionLynx (dual analytical/prep)
Mass Spec Detector:	Waters-Micromass ZQ
PDA Detector:	Waters 2996 PDA

Analytical conditions:

Eluent A:	H_2O (0.1% Formic Acid)
Eluent B:	CH_3CN (0.1% Formic Acid)
Gradient:	5-95% eluent B
Flow:	1.5 ml/min
Column:	Synergi 4µm Max-RP C_{12}, 80A, 50 x 4.6 mm (Phenomenex)

MS conditions:

Capillary voltage:	3.5 kV
Cone voltage:	30 V
Source Temperature:	120 °C
Desolvation Temperature:	300 °C

Platform System 2

HPLC System:	Waters 2795
Mass Spec Detector:	Micromass Platform LC
PDA Detector:	Waters 2996 PDA

<u>Acidic Analytical conditions:</u>

Eluent A:	H_2O (0.1% Formic Acid)
Eluent B:	CH_3CN (0.1% Formic Acid)
Gradient:	5-95% eluent B over 3.5 minutes
Flow:	1.5 ml/min
Column:	Phenomenex Synergi 4µ Max-RP 80A, 50x4.6mm

<u>Basic Analytical conditions:</u>

Eluent A:	H_2O (10mM NH_4HCO_3 buffer adjusted to pH=9.5 with NH_4OH)
Eluent B:	CH_3CN
Gradient:	05-95% eluent B over 3.5 minutes
Flow:	1.5 ml/min
Column:	Waters XTerra MS C_{18} 5µm 4.6x50mm

<u>Polar Analytical conditions:</u>

Eluent A:	H_2O (0.1% Formic Acid)
Eluent B:	CH_3CN (0.1% Formic Acid)
Gradient:	00-50% eluent B over 3 minutes
Flow:	1.5 ml/min
Column:	Phenomenex Synergi 4µ Hydro 80A, 50x4.6mm

<u>MS conditions:</u>

Capillary voltage:	3.5 kV
Cone voltage:	30 V
Source Temperature:	120 °C
Scan Range:	165-700 amu
Ionisation Mode:	ElectroSpray Negative, Positive or Positive & Negative

FractionLynx System 2

System:	Waters FractionLynx (dual analytical/prep)
HPLC Pump:	Waters 2525
Injector-Autosampler:	Waters 2767
Mass Spec Detector:	Waters-Micromass ZQ
PDA Detector:	Waters 2996 PDA

Analytical conditions:

Eluent A:	H_2O (0.1% Formic Acid)
Eluent B:	CH_3CN (0.1% Formic Acid)
Gradient:	5-95% eluent B over 5 minutes
Flow:	2.0 ml/min
Column:	Phenomenex Synergi 4µ Max-RP 80A, 50x4.6mm

Polar Analytical conditions:

Eluent A:	H_2O (0.1% Formic Acid)
Eluent B:	CH_3CN (0.1% Formic Acid)
Gradient:	00-50% eluent B over 5 minutes
Flow:	2.0 ml/min
Column:	Phenomenex Synergi 4µ Max-RP 80A, 50x4.6mm

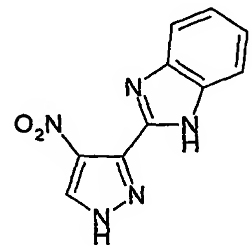
MS conditions:

Capillary voltage:	3.5 kV
Cone voltage:	25 V
Source Temperature:	120 °C
Scan Range:	125-800 amu
Ionisation Mode:	ElectroSpray Positive or ElectroSpray Positive & Negative

The starting materials for each of the Examples are commercially available unless otherwise specified.

EXAMPLE 1

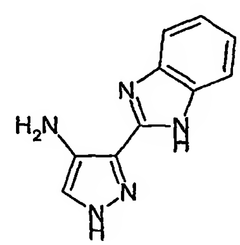
Synthesis of 2-(4-Nitro-1H-pyrazol-3-yl)-1H-benzoimidazole



A mixture of *o*-phenylenediamine (1.51 g, 14.0 mmol), 4-amino-1H-pyrazole-3-carboxylic acid (2.00 g, 12.7 mmol), EDC (2.93 g, 15.3 mmol) and HOBt (2.08 g, 15.3 mmol) in DMF (70 ml) was stirred at ambient temperature for 24 h. The mixture was reduced *in vacuo* and the residue dissolved in AcOH (150 ml) and heated at reflux for 3 h. The solvent was removed *in vacuo*, water (100 ml) added and the resultant solid collected by filtration washing with water. The solid was dried through azeotrope with toluene (3 x 150 ml) yielding 2-(4-nitro-1H-pyrazol-3-yl)-1H-benzoimidazole as a yellow solid (1.44 g, 50%). A 100 mg portion was purified by preparative LC/MS and following evaporation of product containing fractions gave 70 mg of the title compound. (LC/MS: R_t 1.72, $[M+H]^+$ 229.61).

EXAMPLE 2

Synthesis of 3-(1H-Benzoimidazol-2-yl)-1H-pyrazol-4-ylamine

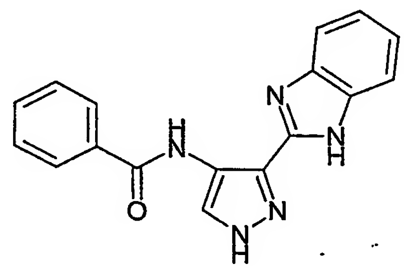


A mixture of 2-(4-nitro-1H-pyrazol-3-yl)-1H-benzoimidazole (1.34 g, 5.85 mmol) and 10% Pd/C (0.13 g) in DMF (200 ml) was subjected to an atmosphere of hydrogen at room temperature for 36 h. The reaction mixture was filtered through a plug of Celite and reduced *in vacuo*. The residue was partitioned between EtOAc and water and the organic portion dried ($MgSO_4$), filtered and reduced *in vacuo*.

The residue was azeotroped with toluene (3 x 150 ml) yielding 3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine as a purple solid (0.32 g, 26%). (LC/MS: R_t 0.97, $[M+H]^+$ 199.62).

EXAMPLE 3

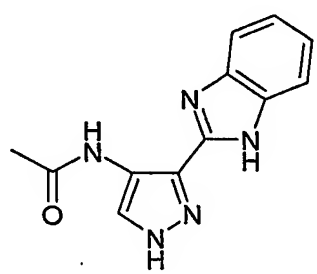
Synthesis of N-[3-(1H-Benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide



A mixture of benzoic acid (34 mg, 0.28 mmol), 3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine (50 mg, 0.25 mmol), EDC (58 mg, 0.30 mmol) and HOBt (40.5 mg, 0.30 mmol) in DMF (5 ml) was stirred at room temperature for 24 h. The solvent was removed *in vacuo*, the crude product purified by preparative LC/MS and following reduction of the product-containing fractions N-[3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide was obtained as a brown solid (23 mg, 30%). (LC/MS: R_t 3.66, $[M+H]^+$ 303.67).

EXAMPLE 4

Synthesis of N-[3-(1H-Benzoimidazol-2-yl)-1H-pyrazol-4-yl]-acetamide

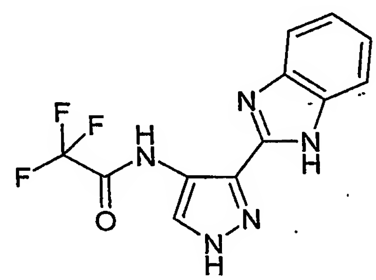


Acetic anhydride (27 μl, 0.28 mmol) was added to a solution of 3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine (50 mg, 0.25 mmol) in pyridine (5 ml)

and the reaction mixture stirred at ambient temperature for 24 h. The mixture was reduced *in vacuo* and the residue purified by flash column chromatography [SiO_2, EtOAc-petrol (1:2.5, 2:1)] to give N-[3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-acetamide as a brown crystalline solid (29 mg, 48%). (LC/MS: R_t 1.70, $[M+H]^+$ 241.64).

EXAMPLE 5

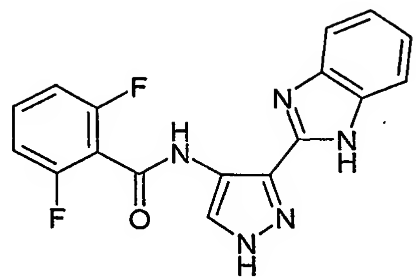
Synthesis of N-[3-(1H-Benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2,2,2-trifluoro-acetamide



Trifluoroacetic anhydride (40 µl, 0.28 mmol) was added to a solution of 3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine (50 mg, 0.25 mmol) in pyridine (5 ml) and the reaction mixture stirred at ambient temperature for 24 h. The mixture was reduced *in vacuo* and the residue purified by flash column chromatography [SiO_2, EtOAc-petrol (1:2)] to afford N-[3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2,2,2-trifluoro-acetamide as a cream solid (23 mg, 32%). (LC/MS: R_t 3.67, $[M+H]^+$ 295.63).

EXAMPLE 6

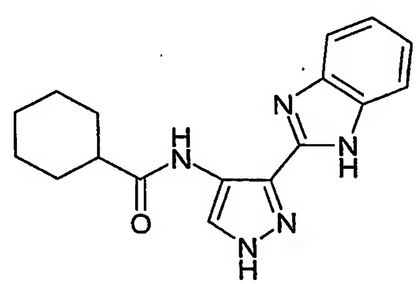
Synthesis of N-[3-(1H-Benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2,6-difluoro-benzamide



A mixture of 2,6-difluorobenzoic acid (43 mg, 0.28 mmol), 3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine (50 mg, 0.25 mmol), EDC (58 mg, 0.30 mmol) and HOBt (40.5 mg, 0.30 mmol) in DMF (10 ml) was stirred at ambient temperature for 24 h. The mixture was reduced *in vacuo*, water (30 ml) added and the resultant solid collected by filtration, dried in the vacuum oven and purified by flash column chromatography [SiO_2, EtOAc-petrol (1:2, 1:1, 3:1)] affording N-[3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2,6-difluoro-benzamide (20 mg, 24%). (LC/MS: R_t 3.29, $[M+H]^+$ 339.64).

EXAMPLE 7

Synthesis of Cyclohexanecarboxylic acid [3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-amide

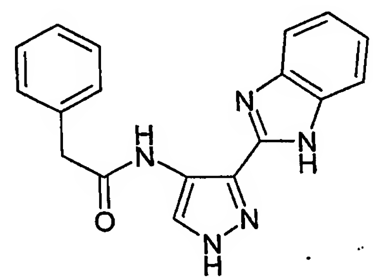


A mixture of cyclohexanecarboxylic acid (36 mg, 0.28 mmol), 3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine (50 mg, 0.25 mmol), EDC (58 mg, 0.30 mmol) and HOBt (41 mg, 0.30 mmol) in DMSO (2 ml) was stirred at ambient temperature for 24 h. The reaction mixture was partitioned between EtOAc (40 ml) and water (40 ml) and the organic portion dried ($MgSO_4$), filtered and reduced *in vacuo*. The residue was purified by flash column chromatography [SiO_2, EtOAc-

petrol (1:4, 1:3, 1:2, 1:1)] affording cyclohexanecarboxylic acid [3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-amide as an off-white solid (25 mg, 32%). (LC/MS: R_t 3.59, $[M+H]^+$ 310.16).

EXAMPLE 8

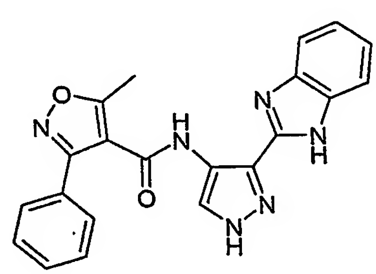
Synthesis of N-[3-(1H-Benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2-phenyl-acetamide



A mixture of phenylacetic acid (38 mg, 0.28 mmol), 3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine (50 mg, 0.25 mmol), EDC (58 mg, 0.30 mmol) and HOBt (41 mg, 0.30 mmol) in DMSO (2 ml) was stirred at ambient temperature for 24 h. The reaction mixture was partitioned between EtOAc (40 ml) and water (40 ml) and the organic portion dried ($MgSO_4$), filtered and reduced *in vacuo*. The residue was purified by flash column chromatography [SiO_2, EtOAc-petrol (1:2, 1:1, 2:1)] to give N-[3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2-phenyl-acetamide as a brown solid (15 mg, 19%). (LC/MS: R_t 3.26, $[M+H]^+$ 318.13).

EXAMPLE 9

Synthesis of 5-Methyl-3-phenyl-isoxazole-4-carboxylic acid [3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-amide



A mixture of 5-methyl-3-phenylisoxazole-4-carboxylic acid (57 mg, 0.28 mmol), 3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine (50 mg, 0.25 mmol), EDC (58 mg, 0.30 mmol) and HOBt (41 mg, 0.30 mmol) in DMSO (2 ml) was stirred at ambient temperature for 24 h. The reaction mixture was partitioned between EtOAc and water and the organic portion dried ($MgSO_4$), filtered and reduced *in vacuo*. The residue was purified by flash column chromatography [SiO_2, EtOAc-petrol (1:2, 1:1, 2:1)] affording 5-methyl-3-phenyl-isoxazole-4-carboxylic acid [3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-amide as a cream solid (15 mg, 16%). (LC/MS: R_t 3.73, $[M+H]^+$ 385.14).

EXAMPLE 10

Synthesis of 2-[4-(2,6-Difluoro-benzoylamino)-1H-pyrazol-3-yl]-1H-benzoimidazole-4-carboxylic acid methyl ester

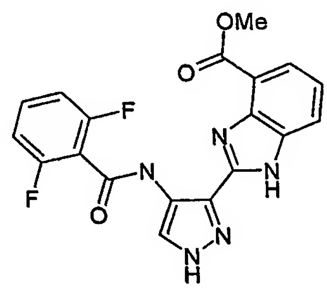
10A. Methyl-2-amino-3-nitrobenzoate

Sodium methoxide (1.50 g, 27.7 mmol) was added to a solution of methyl-2-(acetylamino)-3-nitrobenzoate (1.0 g, 4.2 mmol) in MeOH (30 ml) and the mixture stirred at ambient temperature under nitrogen for 16 h. The reaction was cautiously acidified with concentrated hydrochloric acid then heated at reflux overnight, followed by evaporation and re-evaporation by toluene (2 x 30 ml). The residue was treated with CH_2Cl_2 (50 ml), the insoluble material removed through filtration and the filtrate reduced *in vacuo*. The residue was purified by flash column chromatography [SiO_2, EtOAc-hexane (1:4, 1:0)] affording methyl-2-amino-3-nitrobenzoate (535 mg) as a bright yellow solid.

10B. Methyl 2,3-diaminobenzoate

A mixture of methyl-2-amino-3-nitrobenzoate (530 mg) and 10% Pd/C (55 mg) in EtOH (10 ml) was stirred under an atmosphere of hydrogen at ambient temperature for 16 h. The catalyst was removed by filtration through Celite and the filtrate reduced *in vacuo* to give methyl 2,3-diaminobenzoate (420 mg) as a yellow/brown oil which solidified on standing.

10C. 2-[4-(2,6-Difluoro-benzoylamino)-1H-pyrazol-3-yl]-1H-benzoimidazole-4-carboxylic acid methyl ester



A mixture of 4-(2,6-difluorobenzoylamino)-1H-pyrazole-3-carboxylic acid (690 mg, 2.6 mmol) Example 16D), methyl 2,3-diaminobenzoate (415 mg, 2.6 mmol), EDC (590 mg, 3.1 mmol) and HOBt (415 mg, 3.1 mmol) in DMF (10 ml) was stirred at ambient temperature for 16 h and then reduced *in vacuo*. The residue was partitioned between EtOAc and brine and the organic portion dried ($MgSO_4$), filtered, reduced then crystallised from hot EtOH. The amide intermediate (480 mg) was dissolved in AcOH (10 ml) then heated at reflux for 3 h. The reaction mixture was reduced *in vacuo* and then azeotroped with toluene (2 x 20 ml) to afford 2-[4-(2,6-difluoro-benzoylamino)-1H-pyrazol-3-yl]-1H-benzoimidazole-4-carboxylic acid methyl ester (420 mg) as a fawn coloured solid. (LC/MS: R_t 3.82, $[M+H]^+$ 398).

EXAMPLE 11

Synthesis of 2,6-Difluoro-N-[3-(4-hydroxymethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide and Acetic acid 2-[4-(2,6-difluoro-benzoylamino)-1H-pyrazol-3-yl]-1H-benzoimidazol-4-ylmethyl ester

11A. 2-amino-3-nitrobenzoic acid

A solution of methyl-2-(acetylamino)-3-nitrobenzoate (2.6 g) in EtOH (50 ml) was treated with concentrated hydrochloric acid (10 ml) then heated at reflux for 16 h. The reaction mixture was cooled, reduced *in vacuo* and azeotroped with toluene (2 x 50 ml) to give 2-amino-3-nitrobenzoic acid (1.83 g) as a bright yellow solid.

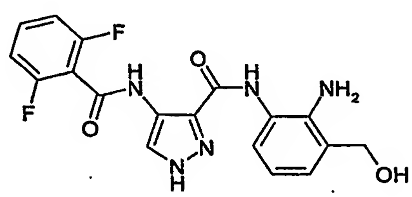
11B. 2-amino-3-nitrobenzyl alcohol

To a solution of 2-amino-3-nitrobenzoic acid (1.82 g, 10.0 mmol) in anhydrous THF (50 ml) was added sodium borohydride (770 mg, 20.0 mmol) followed by boron trifluoride diethyl etherate (2.5 ml, 20 mmol) and the mixture stirred at ambient temperature under a nitrogen atmosphere for 2 h. MeOH was cautiously added until gas evolution had ceased and the mixture reduced *in vacuo*. The residue was partitioned between EtOAc and brine and the organic portion dried ($MgSO_4$) and reduced *in vacuo* to give 2-amino-3-nitrobenzyl alcohol (1.42 g) as a yellow solid.

11C. 2,3-diaminobenzyl alcohol

A mixture of 2-amino-3-nitrobenzyl alcohol (1.4 g) and 10% Pd/C (140 mg) in EtOH (40 ml) and DMF (10 ml) was stirred under an atmosphere of hydrogen at ambient temperature for 18 h. The catalyst was removed by filtration through Celite, the filtrate reduced *in vacuo* and azeotroped with toluene (2 x 50 ml) to give 2,3-diaminobenzyl alcohol (1.15 g) as a dark brown solid.

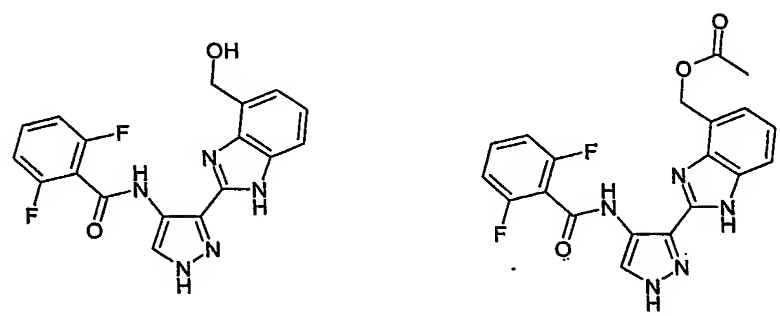
11D. Synthesis of 4-(2,6-difluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid (2-amino-3-hydroxymethyl-phenyl)-amide



A mixture of 4-(2,6-difluorobenzoylamino)-1H-pyrazole-3-carboxylic acid (1.0 g, 3.7 mmol) (Example 16D), 2,3-diaminobenzylalcohol (560 mg, 4.1 mmol), EDC (870 mg, 4.5 mmol) and HOBt (610 mg, 4.5 mmol) in DMF (20 ml) was stirred at ambient temperature for 18 h and then reduced *in vacuo*. The residue was partitioned between EtOAc and brine and the organic portion dried ($MgSO_4$) and reduced *in vacuo*. The residue was purified by flash column chromatography [SiO_2,

EtOAc-hexane (1:1, 2:1)] to give 4-(2,6-difluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid (2-amino-3-hydroxymethyl-phenyl)-amide (860 mg).

11E. Synthesis of 2,6-Difluoro-N-[3-(4-hydroxymethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide and Acetic acid 2-[4-(2,6-difluoro-benzoylamino)-1H-pyrazol-3-yl]-1H-benzoimidazol-4-ylmethyl ester

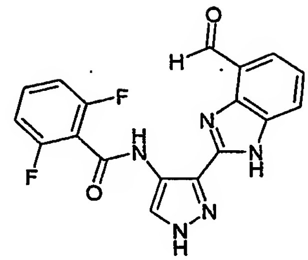


4-(2,6-Difluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid (2-amino-3-hydroxymethyl-phenyl)-amide (100 mg, 0.26 mmol) was dissolved in acetic acid (10 ml) then heated for 10 min at 150 °C (100 W) in a CEM discover microwave synthesiser. The reaction mixture was reduced then azeotroped with toluene (2 x 20 ml). The residue was purified by flash column chromatography [SiO_2, EtOAc-hexane (1:1, 2:1, 3:1)] to give 2,6-difluoro-N-[3-(4-hydroxymethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (25 mg) as an off white solid (LC/MS: R_t 2.70, $[M+H]^+$ 370) and acetic acid 2-[4-(2,6-difluoro-benzoylamino)-1H-pyrazol-3-yl]-1H-benzoimidazol-4-ylmethyl ester (20 mg) as an off white solid. (LC/MS: R_t 3.60, $[M+H]^+$ 412).

EXAMPLE 12

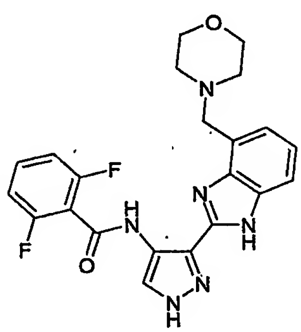
Synthesis of 2,6-Difluoro-N-[3-(4-morpholin-4-yl-methyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide

12A. 2,6-difluoro-N-[3-(4-formyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide



A mixture of 2,6-difluoro-N-[3-(4-hydroxymethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (200 mg, 0.54 mmol) and MnO_2 (500 mg) in CH_2Cl_2/MeOH (5:1, 12 ml) was stirred at ambient temperature for 18 h, then filtered through Celite and reduced *in vacuo*. The residue was purified by flash column chromatography [SiO_2, EtOAc-hexane (1:3, 1:2)] to give 2,6-difluoro-N-[3-(4-formyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (30 mg) as a cream solid.

<u>12B. 2,6-Difluoro-N-[3-(4-morpholin-4-yl-methyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide</u>

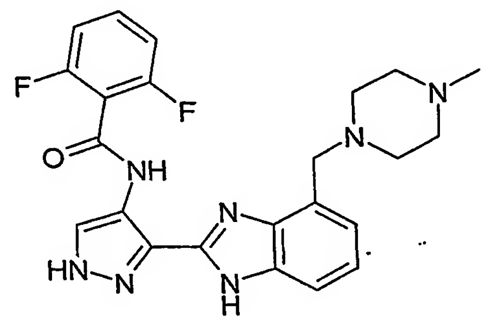


To a solution of 2,6-difluoro-N-[3-(4-formyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (30 mg, 0.08 mmol) and morpholine (14 mg, 0.16 mmol) in CH_2Cl_2 (5 ml) and THF (2 ml) was added 3Å molecular sieves (1 g) followed by sodium triacetoxyborohydride (50 mg, 0.24 mmol) and the mixture stirred at ambient temperature under a nitrogen atmosphere for 2 h. The reaction mixture was filtered through Celite, reduced *in vacuo* then purified by flash column chromatography [SiO_2, EtOAc-hexane (1:1, 1:0), then CH_2Cl_2-MeOH (95:5)]

affording 2,6-difluoro-N-[3-(4-morpholin-4-yl-methyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (13 mg) as a cream solid. (LC/MS: R_t 1.80, $[M+H]^+$ 439).

EXAMPLE 13

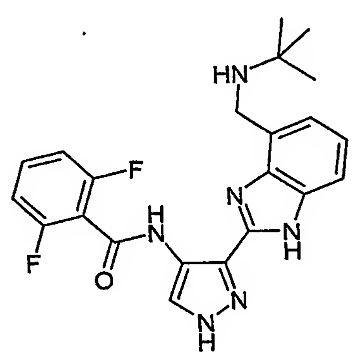
Synthesis of 2,6-Difluoro-N-[3-(N-methyl-piperazinyl-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide



The compound was prepared in a manner analogous to Example 12B, but using N-methylpiperazine in place of morpholine. (LC/MS: R_t 1.93, $[M+H]^+$ 452).

EXAMPLE 14

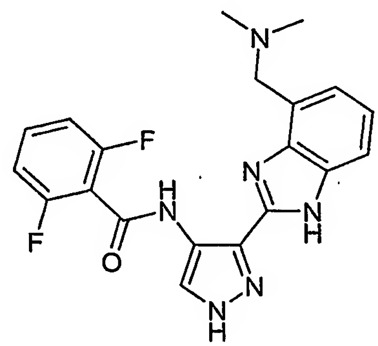
Synthesis of N-{3-[4-(*tert*-Butylamino-methyl)-1H-benzoimidazol-2-yl]-1H-pyrazol-4-yl}-2,6-difluoro-benzamide



The compound was prepared in a manner analogous to Example 12B, but using *tert*-butylamine in place of morpholine. (LC/MS: R_t 2.04, $[M+H]^+$ 425).

EXAMPLE 15

Synthesis of N-[3-(4-Dimethylaminomethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2,6-difluoro-benzamide

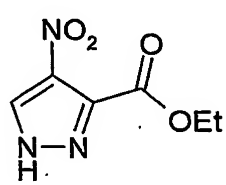


The compound was prepared in a manner analogous to Example 12B, but using 35% dimethylamine in EtOH in place of morpholine. (LC/MS: R_t 1.85, $[M+H]^+$ 397).

EXAMPLE 16

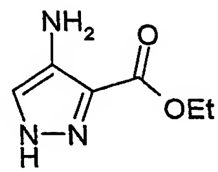
Synthesis of 2-[4-(2,6-Difluoro-benzoylamino)-1H-pyrazol-3-yl]-1H-benzoimidazole-5-carboxylic acid methyl ester

16A. Synthesis of 4-Nitro-1H-pyrazole-3-carboxylic acid ethyl ester



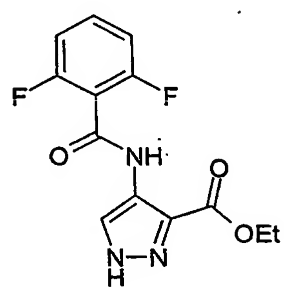
Thionyl chloride (2.90 ml, 39.8 mmol) was slowly added to a mixture of 4-nitro-3-pyrazolecarboxylic acid (5.68 g, 36.2 mmol) in EtOH (100 ml) at ambient temperature and the mixture stirred for 48 h. The mixture was reduced *in vacuo* and dried through azeotrope with toluene to afford 4-nitro-1H-pyrazole-3-carboxylic acid ethyl ester as a white solid (6.42 g, 96%). (^{1}H NMR (400 MHz, DMSO-d_6) δ 14.4 (s, 1H), 9.0 (s, 1H), 4.4 (q, 2H), 1.3 (t, 3H)).

16B. Synthesis of 4-Amino-1H-pyrazole-3-carboxylic acid ethyl ester



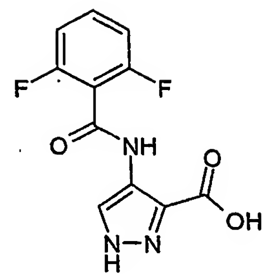
A mixture of 4-nitro-1H-pyrazole-3-carboxylic acid ethyl ester (6.40 g, 34.6 mmol) and 10% Pd/C (650 mg) in EtOH (150ml) was stirred under an atmosphere of hydrogen for 20 h. The mixture was filtered through a plug of Celite, reduced *in vacuo* and dried through azeotrope with toluene to afford 4-amino-1H-pyrazole-3-carboxylic acid ethyl ester as a pink solid (5.28 g, 98%). (^{1}H NMR (400 MHz, DMSO-d_6) δ 12.7 (s, 1H), 7.1 (s, 1H), 4.8 (s, 2H), 4.3 (q, 2H), 1.3 (t, 3H)).

<u>16C. Synthesis of 4-(2,6-Difluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid ethyl ester</u>



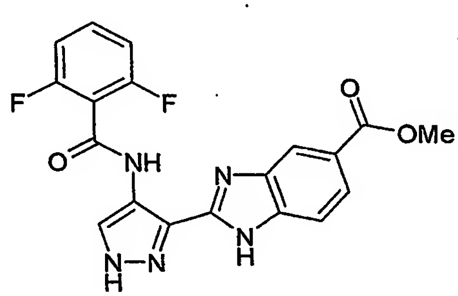
A mixture of 2,6-difluorobenzoic acid (6.32 g, 40.0 mmol), 4-amino-1H-pyrazole-3-carboxylic acid ethyl ester (5.96 g, 38.4 mmol), EDC (8.83 g, 46.1 mmol) and HOBt (6.23 g, 46.1 mmol) in DMF (100 ml) was stirred at ambient temperature for 6 h. The mixture was reduced *in vacuo*, water added and the solid formed collected by filtration and air-dried to give 4-(2,6-difluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid ethyl ester as the major component of a mixture (15.3 g). (LC/MS: R_t 3.11, $[M+H]^+$ 295.99).

<u>16D. Synthesis of 4-(2,6-Difluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid</u>



A mixture of 4-(2,6-difluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid ethyl ester (10.2 g) in 2 M aqueous NaOH/MeOH (1:1, 250 ml) was stirred at ambient temperature for 14 h. Volatile materials were removed *in vacuo*, water (300 ml) added and the mixture taken to pH 5 using 1M aqueous HCl. The resultant precipitate was collected by filtration and dried through azeotrope with toluene to afford 4-(2,6-difluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid as a pink solid (5.70 g). (LC/MS: R_t 2.33, $[M+H]^+$ 267.96).

<u>16E. Synthesis of 2-[4-(2,6-Difluoro-benzoylamino)-1H-pyrazol-3-yl]-1H-benzoimidazole-5-carboxylic acid methyl ester</u>

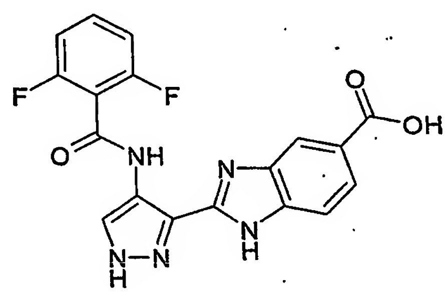


A mixture of 4-(2,6-difluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid (500 mg, 1.87 mmol), methyl 3,4-diaminobenzoate (375 mg, 2.25 mmol), EDC (430 mg, 2.25 mmol) and HOBt (305 mg, 2.25 mmol) in DMF (5 ml) was stirred at ambient temperature for 12 h. The residue was reduced *in vacuo* and then dissolved in the minimum amount of methanol and petroleum ether added to give the intermediate amide as a pink solid which was collected by filtration (427 mg). (LC/MS: R_t 3.24, $[M+H]^+$ 416.02).

A mixture of the amide (150 mg, 0.36 mmol) in glacial acetic acid (4 ml) was heated in the microwave (100 W) at 120 °C for 10 mins. The mixture was reduced *in vacuo* and petroleum ether (3 ml) and methanol (2 ml) added forming a precipitate, which was collected by filtration to give 2-[4-(2,6-difluoro-benzoylamino)-1H-pyrazol-3-yl]-1H-benzoimidazole-5-carboxylic acid methyl ester (96 mg, 67%) as a pink solid. (LC/MS: R_t 3.67, $[M+H]^+$ 397.99).

EXAMPLE 17

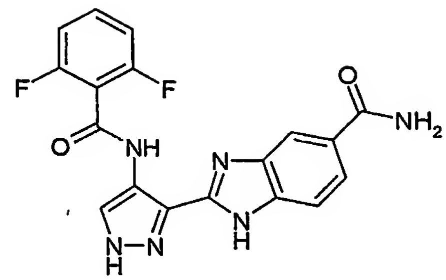
Synthesis of 2-[4-(2,6-Difluoro-benzoylamino)-1H-pyrazol-3-yl]-1H-benzoimidazole-5-carboxylic acid



A mixture of 2-[4-(2,6-difluoro-benzoylamino)-1H-pyrazol-3-yl]-1H-benzoimidazole-5-carboxylic acid methyl ester (12.0 mg, 0.03 mmol) in 2 M aqueous NaOH/MeOH (1:1, 4 ml) was stirred at ambient temperature for 14 h. The mixture was reduced *in vacuo*, water (5 ml) added and the mixture taken to pH 4 using 1 M aqueous HCl. The precipitate formed was collected by filtration and dried under vacuum to give 2-[4-(2,6-difluoro-benzoylamino)-1H-pyrazol-3-yl]-1H-benzoimidazole-5-carboxylic acid as a pale coloured solid (6 mg, 52%). (LC/MS: R_t 2.88, $[M+H]^+$ 383.97).

EXAMPLE 18

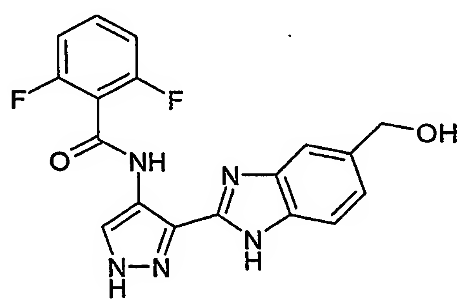
Synthesis of 2-[4-(2,6-Difluoro-benzoylamino)-1H-pyrazol-3-yl]-1H-benzoimidazole-5-carboxylic acid amide



To a mixture of 2-[4-(2,6-difluoro-benzoylamino)-1*H*-pyrazol-3-yl]-1*H*-benzoimidazole-5-carboxylic acid (100 mg, 0.26 mmol), EDC (75 mg, 0.39 mmol) and HOBt (53 mg, 0.39 mmol) in DMF (1.5 ml) was successively added diisopropylethylamine (0.15 ml, 1.04 mmol) and ammonium chloride (28 mg, 0.52 mmol). The mixture was stirred at ambient temperature for 48 h and then reduced *in vacuo*. Water was added and the precipitate formed collected by filtration and dried through azeotrope with toluene to afford 2-[4-(2,6-difluoro-benzoylamino)-1H-pyrazol-3-yl]-1H-benzoimidazole-5-carboxylic acid amide (49 mg, 49%) as a beige solid. (LC/MS: R_t 2.54, $[M+H]^+$ 382.99).

EXAMPLE 19

Synthesis of 2,6-Difluoro-N-[3-(5-hydroxymethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide



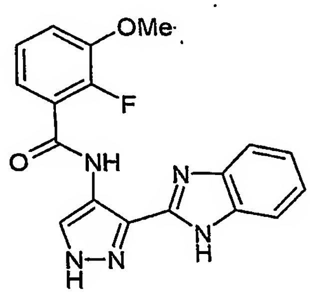
A mixture of 4-(2,6-difluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid (584 mg, 2.19 mmol), (3,4-diamino-phenyl)-methanol (332 mg, 2.40 mmol), EDC (504 mg, 2.63 mmol) and HOBt (355 mg, 2.63 mmol) in DMF (15 ml) was stirred at ambient temperature for 20 h. The mixture was reduced *in vacuo* and the residue taken up in EtOAc, washed with water and brine and the organic portion dried

($MgSO_4$) and reduced *in vacuo* to give the intermediate amide (591 mg) as a brown solid. (LC/MS: R_t 2.34, $[M+H]^+$ 388.00).

A mixture of the amide (575 mg) in glacial AcOH (4 ml) was heated in the microwave (80 W) at 90 °C for 20 min. The mixture was poured into water and the solid formed collected by filtration. The residue was taken up in MeOH (10 ml) and stirred in the presence of NaOMe (320 mg, 5.90 mmol) for 30 min. The mixture was reduced *in vacuo*, taken up in EtOAc and washed with water and brine, dried ($MgSO_4$) and reduced *in vacuo*. The residue was purified by column chromatography [SiO_2, EtOAc] to give 2,6-difluoro-N-[3-(5-hydroxymethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide as a white solid (78 mg, 10% over two steps). (LC/MS: R_t 2.45, $[M+H]^+$ 370.05).

EXAMPLE 20

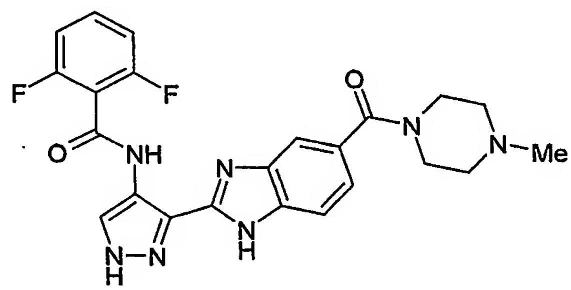
Synthesis of N-[3-(1H-Benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2-fluoro-3-methoxy-benzamide



A mixture of 2-fluoro-3-methoxybenzoic acid (47 mg, 0.28 mmol), 3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine (50 mg, 0.25 mmol), EDC (58 mg, 0.30 mmol) and HOBt (41 mg, 0.30 mmol) in DMF (1.5 ml) was stirred at ambient temperature for 20 h. The reaction mixture was poured into water (30 ml) and the resultant solid collected by filtration and purified by re-crystallisation from MeOH/petrol to yield N-[3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2-fluoro-3-methoxy-benzamide (7 mg, 8%) as a grey solid. (LC/MS: R_t 3.63, $[M+H]^+$ 352.00).

EXAMPLE 21

Synthesis of 2,6-Difluoro-N-{3-[5-(4-methyl-piperazine-1-carbonyl)-1H-benzoimidazol-2-yl]-1H-pyrazol-4-yl}-benzamide

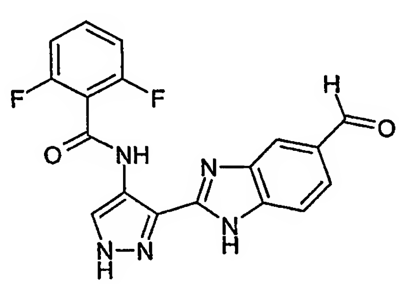


A mixture of 2-[4-(2,6-difluoro-benzoylamino)-1H-pyrazol-3-yl]-1H-benzoimidazole-5-carboxylic acid (115 mg, 0.30 mmol), 1-methyl-piperazine (50.0 μL, 0.45 mmol), EDC (104 mg, 0.54 mmol) and HOBt (73.0 mg, 0.54 mmol) in DMF (5 ml) was stirred at ambient temperature for 14 h. The residue was reduced *in vacuo*, taken up in EtOAc and washed with water and brine, dried ($MgSO_4$) and reduced *in vacuo* to give 2,6-difluoro-N-{3-[5-(4-methyl-piperazine-1-carbonyl)-1H-benzoimidazol-2-yl]-1H-pyrazol-4-yl}-benzamide (37 mg, 26%) as a pale yellow solid. (LC/MS: R_t 1.78, $[M+H]^+$ 466.09).

EXAMPLE 22

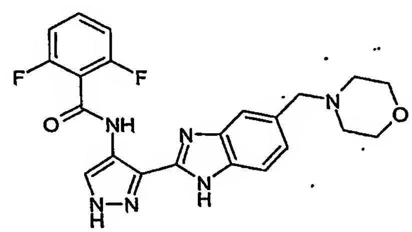
Synthesis of 2,6-Difluoro-N-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide

22A. Synthesis of 2,6-Difluoro-N-[3-(5-formyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide



A mixture of 2,6-difluoro-N-[3-(5-hydroxymethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (800 mg, 2.17 mmol) and MnO_2 (5.00 g, 57.5 mmol) in CH_2Cl_2/MeOH (10:1, 110 ml) was stirred at ambient temperature for 5 days. The mixture was filtered through a plug of Celite washing with MeOH and the filtrate reduced *in vacuo* to give 2,6-difluoro-N-[3-(5-formyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (380 mg, 48%) as a yellow solid. (LC/MS: R_t 3.41, $[M+H]^+$ 368.04).

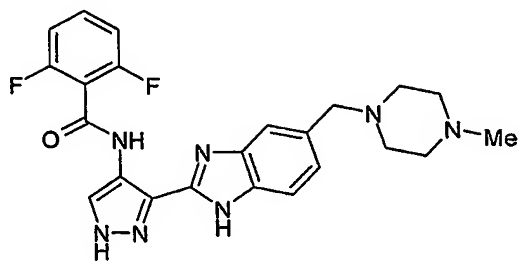
22B. Synthesis of 2,6-Difluoro-N-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide



To a mixture of 2,6-difluoro-N-[3-(5-formyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (75.0 mg, 0.20 mmol) in anhydrous THF (5 ml) stirring at ambient temperature was successively added 3Å molecular sieves, morpholine (35 µL, 0.40 mmol) and triacetoxy sodiumborohydride (127 mg, 0.60 mmol). The mixture was stirred for 4 h, MeOH (3 ml) added and then the mixture reduced *in vacuo*. The residue was taken up in EtOAc, washed with water and brine, dried ($MgSO_4$), reduced *in vacuo* and then purified through preparative LC/MS to give 2,6-difluoro-N-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (9 mg, 10%) as a white solid. (LC/MS: R_t 1.90, $[M+H]^+$ 439.09).

EXAMPLE 23

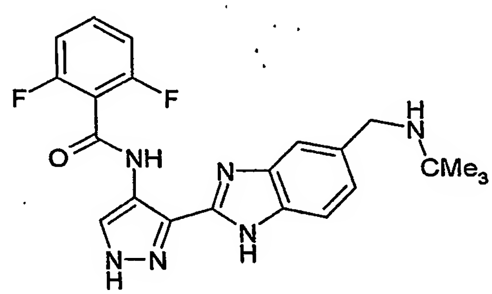
Synthesis of 2,6-Difluoro-N-{3-[5-(4-methyl-piperazin-1-ylmethyl)-1H-benzoimidazol-2-yl]-1H-pyrazol-4-yl}-benzamide



The compound was prepared in a manner analogous to Example 22B, however using 1-methyl piperazine (44.0 μL, 0.40 mmol) as the amine fragment to give 2,6-difluoro-N-{3-[5-(4-methyl-piperazin-1-ylmethyl)-1H-benzoimidazol-2-yl]-1H-pyrazol-4-yl}-benzamide (4 mg, 5%) as a yellow solid. (LC/MS: R_t 1.66, $[M+H]^+$ 452.11)

EXAMPLE 24

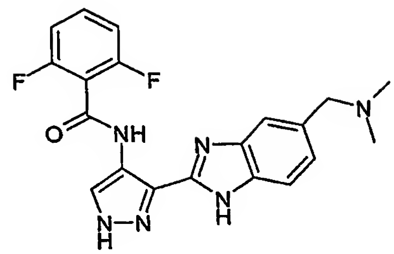
Synthesis of N-{3-[5-(*tert*-Butylamino-methyl)-1H-benzoimidazol-2-yl]-1H-pyrazol-4-yl}-2,6-difluoro-benzamide



The compound was prepared in a manner analogous to Example 22B, however using *tert*-butylamine (42 μL, 0.40 mmol) as the amine fragment to give N-{3-[5-(*tert*-butylamino-methyl)-1H-benzoimidazol-2-yl]-1H-pyrazol-4-yl}-2,6-difluoro-benzamide (5 mg, 6%) as a white solid. (LC/MS: R_t 2.00, $[M+H]^+$ 425.11)

EXAMPLE 25

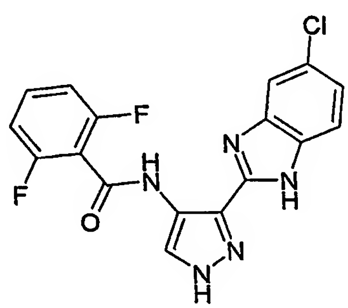
Synthesis of N-[3-(5-Dimethylaminomethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2,6-difluoro-benzamide



The compound was prepared in a manner analogous to Example 22B, however using 2,6-difluoro-N-[3-(5-formyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (57.4 mg, 0.16 mmol), dry THF (5 ml), 3Å molecular sieves, dimethylamine (35% in EtOH) (55 μL, 0.31 mmol) and triacetoxy sodium borohydride (100 mg, 0.47 mmol) to give N-[3-(5-dimethylaminomethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2,6-difluoro-benzamide (11 mg, 18%) as a yellow solid. (LC/MS: R_t 2.85, $[M+H]^+$ 397.17).

EXAMPLE 26

Synthesis of N-[3-(5-Chloro-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2,6-difluoro-benzamide

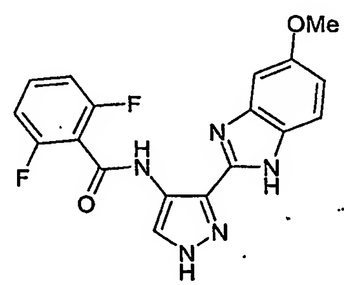


A mixture of 4-(2,6-difluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid (50 mg, 0.18 mmol), 4-chlorophenylenediamine (30 mg, 0.21 mmol), EDC (45 mg, 0.22 mmol) and HOBt (30 mg, 0.22 mmol) in DMF (5 ml) was stirred at ambient temperature for 18 h. The reaction mixture was reduced *in vacuo* and the residue purified by column chromatography [SiO_2, EtOAc/hexane (1:1)] to give the intermediate amide. A mixture of the amide in AcOH (2 ml) was heated in a microwave (50W) at 140 °C for 15 min and then reduced *in vacuo*. The residue was

purified by column chromatography [SiO_2, EtOAc/petrol (1:1)] to give N-[3-(5-chloro-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2,6-difluoro-benzamide (20 mg) as a fawn solid. (LC/MS: R_t 4.16, $[M+H]^+$ 374).

EXAMPLE 27

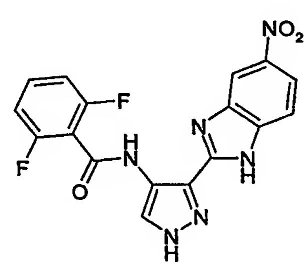
Synthesis of 2,6-Difluoro-N-[3-(5-methoxy-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide



The compound was prepared in a manner analogous to Example 26, but using 4-methoxyphenylenediamine (28 mg, 0.21 mmol) as the amine fragment to give 2,6-difluoro-N-[3-(5-methoxy-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (25 mg) as a pale brown solid. (LC/MS: R_t 3.26, $[M+H]^+$ 370).

EXAMPLE 28

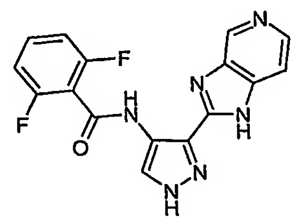
Synthesis of 2,6-Difluoro-N-[3-(5-nitro-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide



The compound was prepared in a manner analogous to Example 26, but using 4-nitrophenylenediamine (32 mg, 0.21 mmol) as the amine fragment to give 2,6-difluoro-N-[3-(5-nitro-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (18 mg). (LC/MS: R_t 3.84, $[M+H]^+$ 385).

EXAMPLE 29

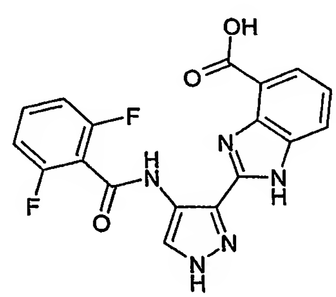
Synthesis of 2,6-Difluoro-N-[3-(1H-imidazo[4,5-c]pyridin-2-yl)-1H-pyrazol-4-yl]-benzamide



The compound was prepared in a manner analogous to Example 26, but using 3,4-diaminopyridine (22 mg, 0.21 mmol) as the amine fragment to give 2,6-difluoro-N-[3-(1H-imidazo[4,5-c]pyridin-2-yl)-1H-pyrazol-4-yl]-benzamide (13 mg) as a brown solid. (LC/MS: R_t 4.16, $[M+H]^+$ 341).

EXAMPLE 30

Synthesis of 2-[4-(2,6-Difluoro-benzoylamino)-1H-pyrazol-3-yl]-1H-benzoimidazole-4-carboxylic acid

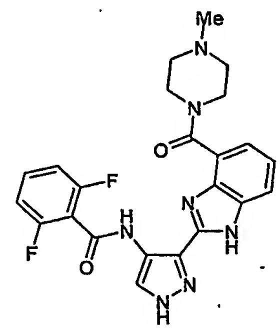


A solution of 2-[4-(2,6-difluoro-benzoylamino)-1H-pyrazol-3-yl]-1H-benzoimidazole-4-carboxylic acid methyl ester (220 mg, 0.55 mmol) in THF/water (1:1, 10 ml) was treated with lithium hydroxide hydrate (70 mg, 1.66 mmol) and the mixture stirred at ambient temperature for 18 h. The volatiles were removed *in vacuo*, the mixture acidified to pH5 by the addition of 2M aqueous hydrochloric acid and the solid formed collected by filtration, washed with water then dried under vacuum to give 2-[4-(2,6-difluoro-benzoylamino)-1H-pyrazol-3-yl]-1H-

benzoimidazole-4-carboxylic acid (165 mg) as a brown solid. (LC/MS: R_t 3.28, $[M+H]^+$ 384).

EXAMPLE 31

Synthesis of 2,6-Difluoro-N-{3-[4-(4-methyl-piperazine-1-carbonyl)-1H-benzoimidazol-2-yl]-1H-pyrazol-4-yl}-benzamide

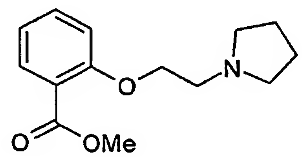


A mixture of 2-[4-(2,6-difluoro-benzoylamino)-1H-pyrazol-3-yl]-1H-benzoimidazole-4-carboxylic acid (50 mg, 0.13 mmol), N-methylpiperazine (20 µl, 0.18 mmol), EDC (30 mg, 0.15 mmol) and HOBt (22 mg, 0.15 mmol) in DMF (5 ml) was stirred at ambient temperature for 18 h. The mixture was reduced *in vacuo* and the residue purified by flash column chromatography [SiO_2, CH_2Cl_2/MeOH (95:5, 90:10)] to give 2,6-difluoro-N-{3-[4-(4-methyl-piperazine-1-carbonyl)-1H-benzoimidazol-2-yl]-1H-pyrazol-4-yl}-benzamide (14 mg) as a cream solid. (LC/MS: R_t 2.21, $[M+H]^+$ 466).

EXAMPLE 32

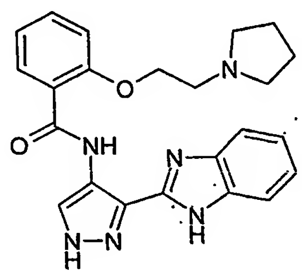
Synthesis of N-[3-(1H-Benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2-(2-pyrrolidin-1-yl-ethoxy)-benzamide

32A. Synthesis of 2-(2-Pyrrolidin-1-yl-ethoxy)-benzoic acid methyl ester



To a mixture of triphenylphosphine (0.79 g, 3.0 mmol) in THF (15 ml) was successively added diisopropylazodicarboxylate (0.61 g, 3.0 mmol) followed by methyl salicylate (0.46 g, 3.0 mmol) and the resultant mixture stirred at ambient temperature for 1 h. 1-(2-Hydroxyethyl)-pyrrolidine (0.35 g, 3.0 mmol) was then added drop-wise and the reaction mixture left stirring at ambient temperature for a further 5 h. The reaction mixture was reduced *in vacuo* and purified by flash column chromatography [SiO_2, EtOAc/MeOH (3:1, 1:1)] to give 2-(2-pyrrolidin-1-yl-ethoxy)-benzoic acid methyl ester as a clear yellow oil (446 mg, 60 %). (LC/MS: R_t 1.58, $[M+H]^+$ 250.05).

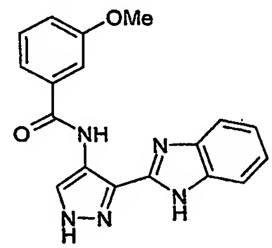
32B. Synthesis of N-[3-(1H-Benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2-(2-pyrrolidin-1-yl-ethoxy)-benzamide



2-(2-Pyrrolidin-1-yl-ethoxy)-benzoic acid methyl ester (125 mg, 0.50 mmol) and lithium hydroxide (21 mg, 0.50 mmol) were dissolved in THF/H_20 (1:1, 2 ml) and the mixture stirred at ambient temperature for 20 h. The reaction mixture was reduced *in vacuo* and azeotroped with toluene (3 x 5 ml) to give a white solid, which was dissolved in water (1 ml) and acidified with 2 M aqueous HCl (1 ml). The resulting solution was reduced *in vacuo* and azeotroped with toluene (3 x 5 ml) to give a pale yellow gel, which was combined with 3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine (100 mg, 0.50 mmol), EDC (116 mg, 0.60 mmol) and HOBt (81 mg, 0.60 mmol) and stirred at ambient temperature in DMF (3 ml) for 20 h. The reaction mixture was reduced *in vacuo* and purified by flash column chromatography [SiO_2, CH_2Cl_2/MeOH (95:5, 87.5:12.5) then 120 DMAW] to give N-[3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2-(2-pyrrolidin-1-yl-ethoxy)-benzamide (63 mg, 30%) as a pale pink solid. (LC/MS: R_t 2.08, $[M+H]^+$ 417.11).

EXAMPLE 33

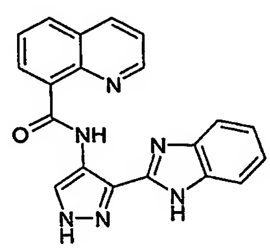
Synthesis of N-[3-(1H-Benzoimidazol-2-yl)-1H-pyrazol-4-yl]-3-methoxy-benzamide



A mixture of 3-methoxybenzoic acid (84 mg, 0.55 mmol), 3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine (100 mg, 0.50 mmol), EDC (116 mg, 0.60 mmol) and HOBt (81 mg, 0.60 mmol) was stirred at ambient temperature in DMSO (3 ml) for 20 h. The reaction mixture was poured into water (30 ml) and the resultant solid was collected by filtration and purified by flash column chromatography [SiO_2, 120 DMAW] to yield N-[3-(1H-Benzoimidazol-2-yl)-1H-pyrazol-4-yl]-3-methoxy-benzamide as a pale pink-grey solid (21 mg, 13 %). (LC/MS: R_t 3.81, $[M+H]^+$ 334.03).

EXAMPLE 34

Synthesis of Quinoline-8-carboxylic acid [3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-amide

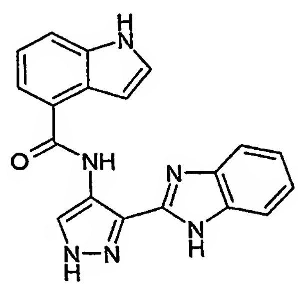
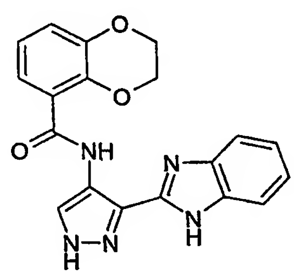
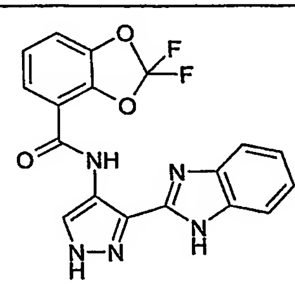


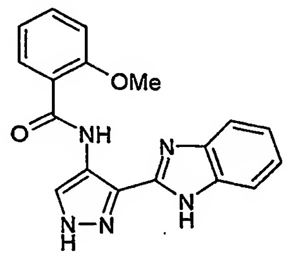
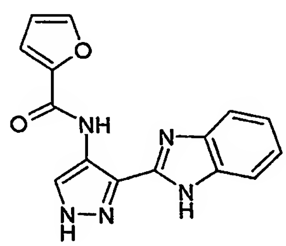
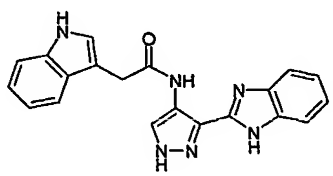
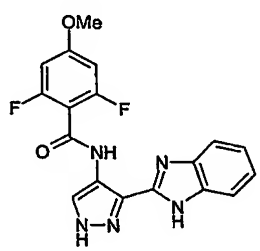
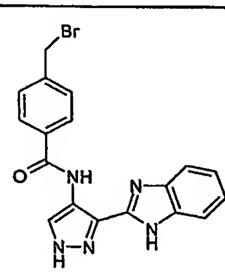
A mixture of quinoline-8-carboxylic acid (104 mg, 0.60 mmol), 3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine (100 mg, 0.50 mmol), EDC (116 mg, 0.60 mmol) and HOBt (81 mg, 0.60 mmol) was stirred at room temperature in DMF (1.5 ml) for 20 h. The reaction mixture was purified by preparative LC/MS to

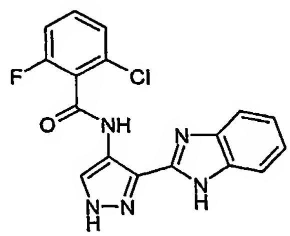
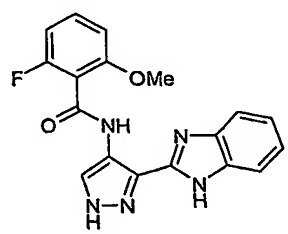
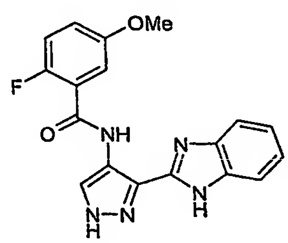
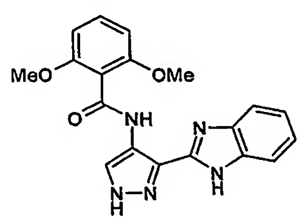
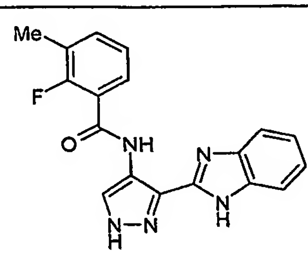
give quinoline-8-carboxylic acid [3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-amide (11 mg, 6%) as a brown solid. (LC/MS: R_t 3.85, $[M+H]^+$ 355.11).

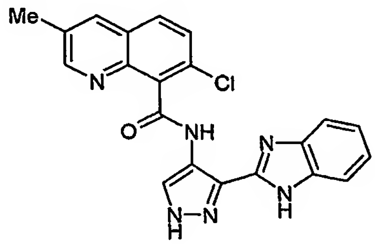
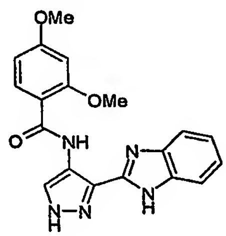
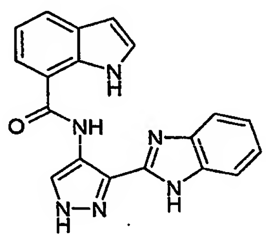
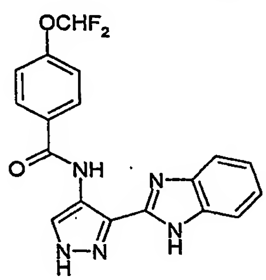
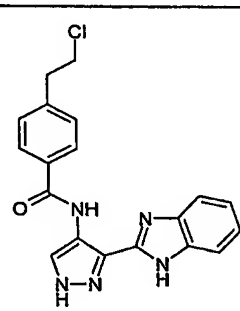
EXAMPLES 35 – 67

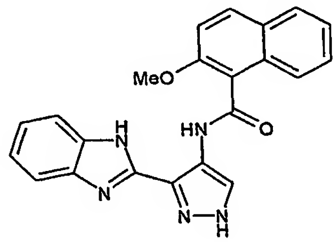
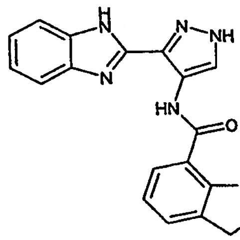
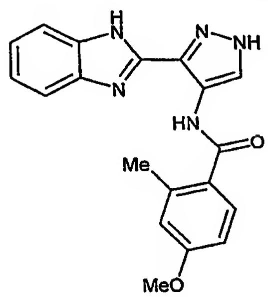
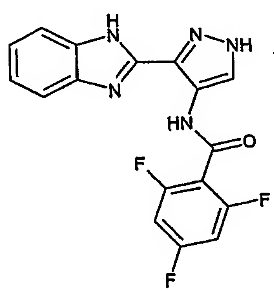
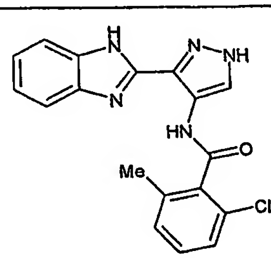
By following the procedure described in Example 34, but using the appropriate carboxylic acid in place of quinoline-8-carboxylic acid, the following compounds were prepared.

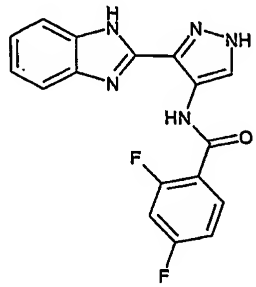
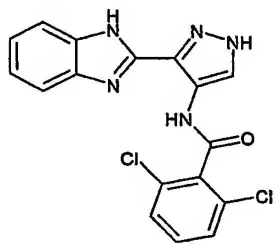
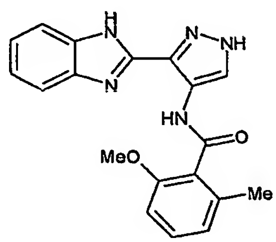
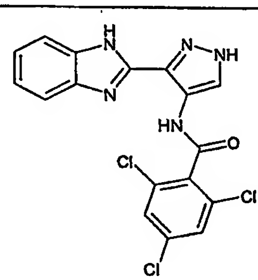
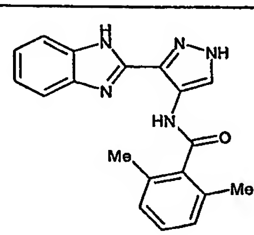
Example	COMPOUND	R_t	*m/z* $[M+H]^+$
35		3.28	343.07
36		3.54	362.07
37		4.26	384.04

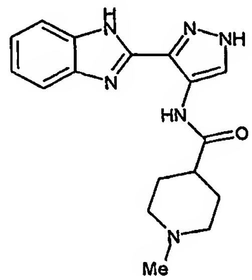
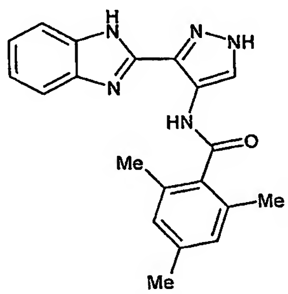
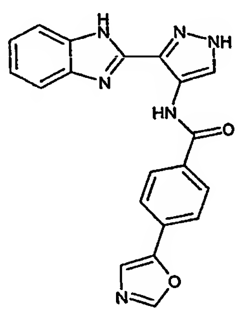
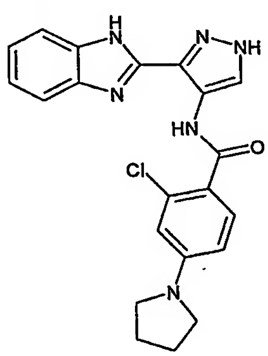
Example	COMPOUND	R_t	m/z [M+H]$^+$
38		3.51	334
39		2.98	294
40		3.09	357
41		3.32	370
42		3.45	397

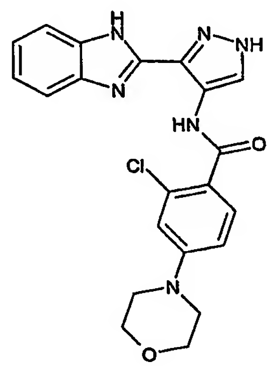
Example	COMPOUND	R_t	m/z $[M+H]^+$
43		3.50	356
44		3.32	352
45		3.88	352.03
46		3.07	364.06
47		4.06	336.01

Example	COMPOUND	R_t	m/z $[M+H]^+$
48		2.85	403.03
49		3.58	364.11
50		4.22	343.07
51		3.91	370.07
52		4.11	366.08

Example	COMPOUND	R_t	m/z $[M+H]^+$
53		3.53	346.06
54		3.82	384.09
55		3.77	348.10
56		3.62	358.07
57		3.75	352.07

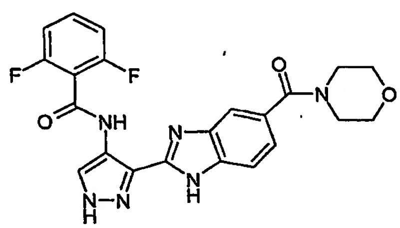
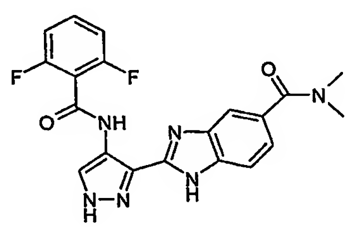
Example	COMPOUND	R_t	m/z $[M+H]^+$
58		3.95	340.06
59		2.96	372/374
60		3.49	348.14
61		4.46	406.00
62		3.78	332.10

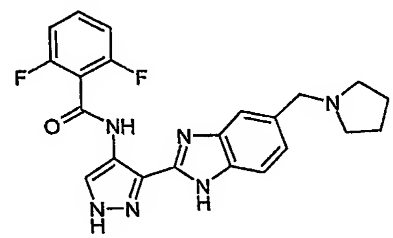
Example	COMPOUND	R_t	*m/z* $[M+H]^+$
63		0.98	325.13
64		4.12	346.13
65		3.44	371.07
66		4.44	407.11

Example	COMPOUND	R_t	m/z [M+H]$^+$
67		3.47	423.12

EXAMPLES 68 – 70

By following the methods described in Examples 21 and 22, the following compounds were prepared.

Example	Method	COMPOUND	R_t	m/z [M+H]$^+$
68	Example 21		2.82	453.07
69	Example 21		2.84	411.08

Example	Method	COMPOUND	R_t	m/z $[M+H]^+$
70	Example 22		1.91	423.14

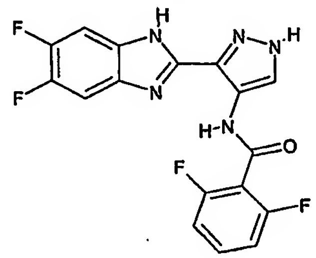
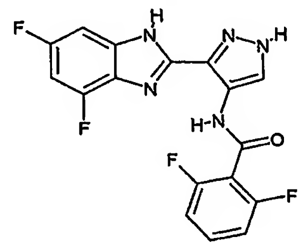
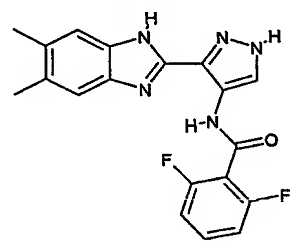
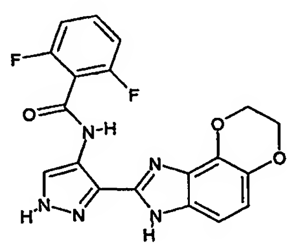
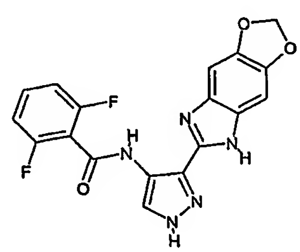
EXAMPLES 71 - 75

General Procedure A

A mixture of 4-(2,6-difluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid (0.134 g, 0.50 mmol), appropriate benzene-1,2-diamine (0.60 mmol), EDC (0.116 g, 0.60 mmol) and HOBt (0.081 g, 0.60 mmol) in DMF (3 ml) was stirred at ambient temperature for 18 h. The reaction mixture was reduced *in vacuo* and the residue partitioned between ethyl acetate (50 ml) and saturated aqueous sodium bicarbonate solution (50 ml). The organic layer was washed with brine, dried ($MgSO_4$) and reduced *in vacuo* to give the intermediate amide. Acetic acid (6 ml) was added to the crude amide and the mixture was heated in a microwave (120 W) at 110 °C for 10 min and then reduced *in vacuo*. The residue was purified by preparative LC/MS to give the desired product.

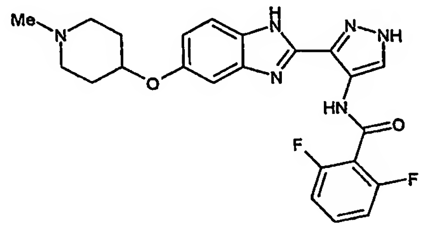
The following compounds were made using General Procedure A:

Example	COMPOUND	R_t	m/z $[M+H]^+$

71		3.03	376.06
72		3.03	376.05
73		2.79	368.17
74		2.57	398.12
75		2.52	384.09

EXAMPLE 76

Synthesis of 2,6-Difluoro-N-{3-[5-(1-methyl-piperidin-4-yloxy)-1H-benzoimidazol-2-yl]-1H-pyrazol-4-yl}-benzamide



3,4-Dinitrofluorobenzene (1.86 g, 10 mmol) and 4-hydroxy-1-methylpiperidine (1.38 g, 12 mmol) were dissolved in THF (20 ml) and stirred at ambient temperature while sodium hydride (60 % dispersion in mineral oil, 0.40 g, 10 mmol) was added in several small portions. The reaction mixture was stirred for one hour and then reduced *in vacuo*, partitioned between ethyl acetate and water, and the organic phase washed with brine, dried ($MgSO_4$) and reduced *in vacuo*. The resulting residue was subject to column chromatography, eluting with 5% MeOH / DCM to give a yellow solid (1.76 g, 2:1 ratio of desired 4-(3,4-dinitro-phenoxy)-1-methyl-piperidine and a side product, 4-(4-fluoro-2-nitro-phenoxy)-1-methyl-piperidine).

A sample of the mixture of products obtained (0.562 g) was dissolved in DMF (10 ml) under an atmosphere of nitrogen. The reaction mixture was then shaken under a hydrogen atmosphere for 40 hours, the solids were removed by filtration and the filtrate reduced *in vacuo* to give a black oil (1:1 mixture of desired 4-(1-methyl-piperidin-4-yloxy)-benzene-1,2-diamine and the reduced side product, 5-fluoro-2-(1-methyl-piperidin-4-yloxy)-phenylamine).

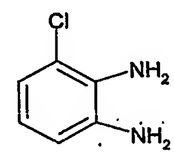
A sample of the black oil (0.221 g) was combined with 4-(2,6-difluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid (0.134 g, 0.50 mmol), EDC (0.116 g, 0.60 mmol) and HOBt (0.081 g, 0.60 mmol) and DMF (3 ml) and the resulting reaction mixture was stirred at ambient temperature for 18 hours. One half of the reaction mixture was subjected to work up conditions: after reducing *in vacuo* the

residue was partitioned between ethyl acetate (50 ml) and saturated aqueous sodium bicarbonate solution (50 ml). The organic layer was washed with brine, dried ($MgSO_4$) and reduced *in vacuo* to give the intermediate amide. Acetic acid (6 ml) was added to the crude amide and the mixture was heated at reflux for 3.5 hours and then reduced *in vacuo*. The residue was purified by preparative LC/MS to give the formate salt of 2,6-difluoro-N-{3-[5-(1-methyl-piperidin-4-yloxy)-1H-benzoimidazol-2-yl]-1H-pyrazol-4-yl}-benzamide (0.035 g) as a brown solid. (LC/MS: R_t 1.82, $[M+H]^+$ 453.30).

EXAMPLE 77

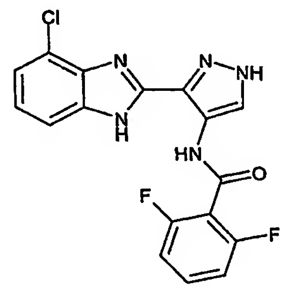
Synthesis of N-[3-(4-Chloro-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2,6-difluoro-benzamide

77A. Synthesis of 3-Chloro-benzene-1,2-diamine



3-Chloro-2-nitro-aniline (0.345 g, 2 mmol) was dissolved in *iso*-propanol (10 ml) and water (2 ml). Catalytic acetic acid (0.1 ml) was added, followed by Raney nickel (0.02 g, as 50 % slurry in H_2O) under a flow of nitrogen. The reaction mixture was then shaken under an atmosphere of hydrogen at ambient temperature for 5 hours and the catalyst was removed by filtration under a nitrogen atmosphere. The filtrate was reduced *in vacuo*, partitioned between ethyl acetate and water, and the organic layer reduced *in vacuo* to give 3-chloro-benzene-1,2-diamine as a brown oil (0.190 g, 67 %). (LC/MS: R_t 1.84, $[M+H]^+$ 143.07).

77B. Synthesis of N-[3-(4-Chloro-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2,6-difluoro-benzamide



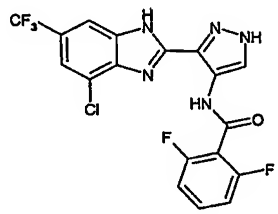
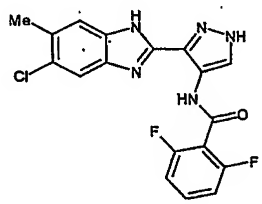
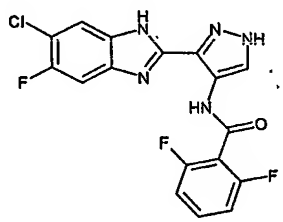
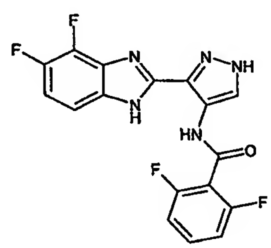
A mixture of 4-(2,6-difluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid (0.134 g, 0.50 mmol), 3-chloro-benzene-1,2-diamine (0.085 g, 0.60 mmol), EDC (0.116 g, 0.60 mmol) and HOBt (0.081 g, 0.60 mmol) in DMF (3 ml) was stirred at ambient temperature for 18 hours. The reaction mixture was reduced *in vacuo* and the residue partitioned between ethyl acetate (50 ml) and saturated aqueous sodium bicarbonate solution (50 ml). The organic layer was washed with brine, dried ($MgSO_4$) and reduced *in vacuo* to give the intermediate amide. Acetic acid (5 ml) was added to the crude amide and the mixture was heated at reflux for 3 hours and then reduced *in vacuo*. The residue was purified by preparative LC/MS to give N-[3-(4-chloro-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2,6-difluoro-benzamide (0.052 g, 28 %) as a brown solid. (LC/MS: R_t 3.18, $[M+H]^+$ 374.09).

EXAMPLES 78 - 81

General Procedure B

A mixture of 4-(2,6-difluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid (100 mg, 0.37 mmol), the relevant diamine (1.2 eq.), EDC (1.2 eq.) and HOAt (1.2 eq.) in DMF (1.2 ml) was stirred at ambient temperature for 16 hours. The reaction was worked up by pouring into water and extracting with EtOAc (x2). The combined organic layers were washed with water again, brine and dried over $MgSO_4$. The product was filtered and evaporated to dryness to leave the intermediate amide as a solid. A mixture of this amide in AcOH (2 ml) was heated in a microwave (50W) at 110 °C until the reaction was complete. The suspension was reduced *in vacuo* and the residue was purified by prep HPLC.

The following compounds were prepared by General Procedure B:

Example	Compound	m/z $[M+H]^+$
78		442, RT 3.51 min
79		389, RT 3.33 min
80		392/394, RT 3.24 min
81		376, RT 3.09 min

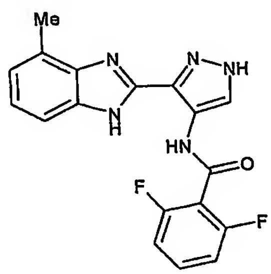
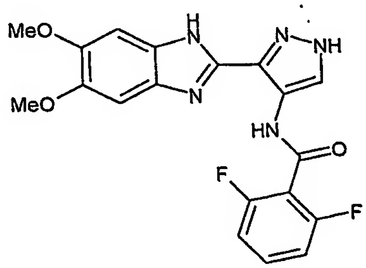
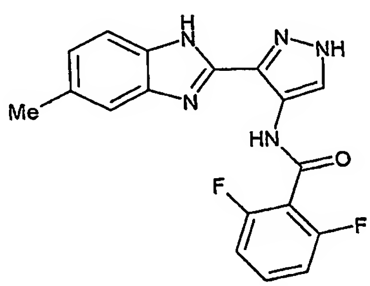
5 EXAMPLES 82 - 86

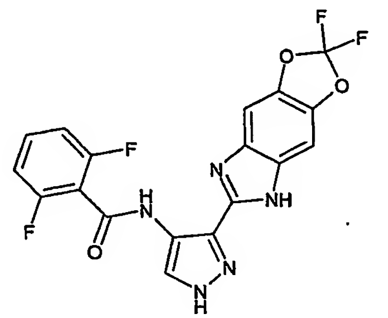
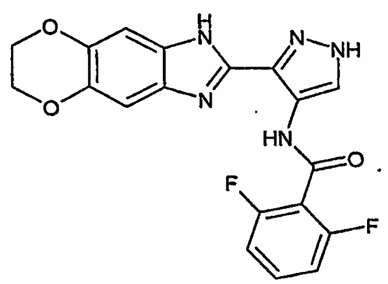
General Procedure C

A mixture of 4-(2,6-difluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid (150 mg, 0.56 mmol), the relevant diamine (1.1 eq.), EDC (1.2 eq.) and HOBt (1.2 eq.)

in DMF (4 ml) was stirred at ambient temperature for 16 hours and then reduced *in vacuo*. The residue was partitioned between EtOAc and saturated aqueous $NaHCO_3$ and the organic portion washed with water, dried ($MgSO_4$) and reduced *in vacuo*. The residue was taken up in AcOH (4 ml) and heated in a microwave (100W) at 120 °C for 10 minutes. The mixture was reduced *in vacuo* and purified by preparative HPLC.

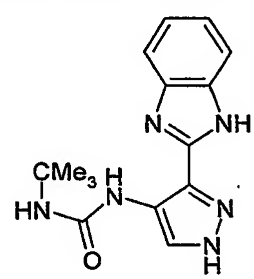
The following compounds were prepared by General Procedure C:

Example	COMPOUND	*m/z* $[M+H]^+$
82		354, RT 2.88 min
83		400, RT 2.16 min
84		354, RT 2.78 min

Example	COMPOUND	m/z $[M+H]^+$
85		420, RT 3.22 min
86		398, RT 2.42 min

EXAMPLE 87

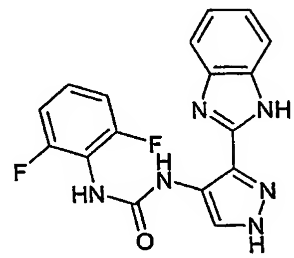
Synthesis of 1-[3-(1H-Benzoimidazol-2-yl)-1H-pyrazol-4-yl]-3-tert-butyl-urea



A mixture or 3-(1H-Benzoimidazol-2-yl)-1H-pyrazol-4-ylamine (100mg, 0.50 mmol), tert-butyl isocyanate (60ul, 0.60 mmol) in DMF (5ml) was stirred at ambient temperature for 4 h. The mixture was reduced *in vacuo*. The residue was purified by preparative LC/MS, and following evaporation, gave 52mg of the title compound as a white solid (35%). (LC/MS: R_t 2.61, $[M+H]^+$ 299.15).

EXAMPLE 88

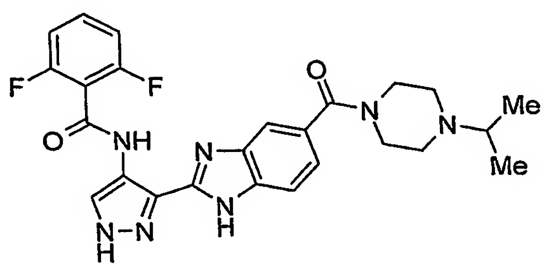
Synthesis of 1-[3-(1H-Benzoimidazol-2-yl)-1H-pyrazol-4-yl]-3-(2,6-difluoro-phenyl)-urea



The compound was prepared in a manner analogous to Example 87, but using 2,6-difluorophenyl isocyanate to give the title compound as a white solid (15mg). (LC/MS: R_t 2.82, $[M+H]^+$ 355).

EXAMPLE 89

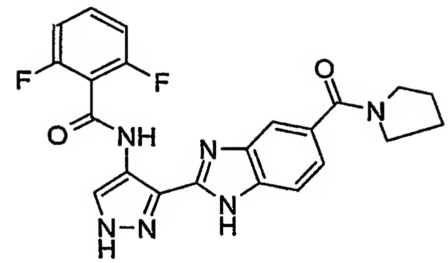
Synthesis of 2,6-Difluoro-N-{3-[5-(4-isopropyl-piperazine-1-carbonyl)-1H-benzoimidazol-2-yl]-1H-pyrazol-4-yl}-benzamide



The compound was prepared in a manner analogous to Example 21 but using 1-isopropylpiperazine as the amine fragment to give 2,6-difluoro-N-{3-[5-(4-isopropyl-piperazine-1-carbonyl)-1H-benzoimidazol-2-yl]-1H-pyrazol-4-yl}-benzamide as a yellow solid (63 mg). (LC/MS: R_t 1.87, $[M+H]^+$ 494.18).

EXAMPLE 90

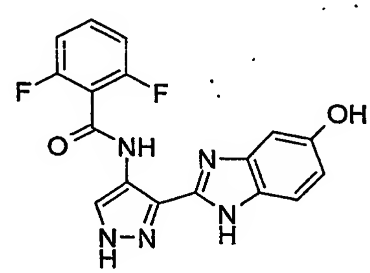
Synthesis of 2,6-Difluoro-N-{3-[5-(pyrrolidine-1-carbonyl)-1H-benzoimidazol-2-yl]-1H-pyrazol-4-yl}-benzamide



The compound was prepared in a manner analogous to Example 21 but using pyrrolidine as the amine fragment to give 2,6-difluoro-N-{3-[5-(pyrrolidine-1-carbonyl)-1H-benzoimidazol-2-yl]-1H-pyrazol-4-yl}-benzamide as a white solid (17 mg). (LC/MS: R_t 3.03, $[M+H]^+$ 437.16).

EXAMPLE 91

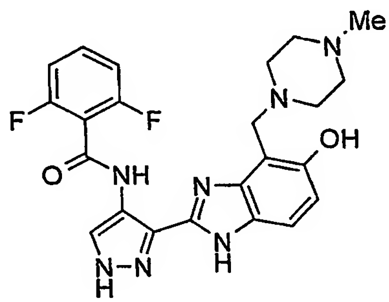
Synthesis of 2,6-Difluoro-N-[3-(5-hydroxy-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide



A mixture of 2,6-difluoro-N-[3-(5-methoxy-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (Example 27) (850 mg) and aluminium (III) chloride (220 mg) in toluene (4 ml) was heated at 80 °C for 3 hours, cooled to ambient temperature and saturated aqueous $NaHCO_3$ (4 ml) followed by 5% aqueous citric acid (4 ml) added. The mixture was extracted with EtOAc and organic extract washed with brine, dried (MgSO4) and reduced *in vacuo*. Residue submitted for preparative LC/MS to give 2,6-difluoro-N-[3-(5-hydroxy-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (22 mg) as a beige solid. (LC/MS: R_t 2.01, $[M+H]^+$ 356.09).

EXAMPLE 92

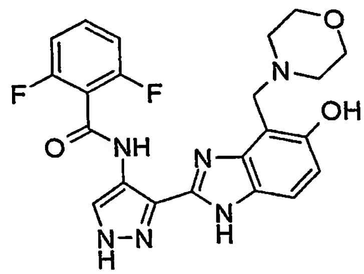
Synthesis of 2,6-Difluoro-N-{3-[5-hydroxy-4-(4-methyl-piperazin-1-ylmethyl)-1H-benzoimidazol-2-yl]-1H-pyrazol-4-yl}-benzamide



A mixture of 2,6-difluoro-N-[3-(5-hydroxy-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (50 mg), 37% aqueous formaldehyde (1 ml) and N-methylpiperazine (150 μL) in benzene (1 ml) was heated in a microwave at 100 °C and 50 W for 10 minutes, reduced *in vacuo* and submitted to preparative LC/MS for purification to give 2,6-difluoro-N-{3-[5-hydroxy-4-(4-methyl-piperazin-1-ylmethyl)-1H-benzoimidazol-2-yl]-1H-pyrazol-4-yl}-benzamide (7 mg) as a yellow solid. (LC/MS: R_t 1.98, $[M+H]^+$ 468.19).

EXAMPLE 93

Synthesis of 2,6-Difluoro-N-[3-(5-hydroxy-4-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide

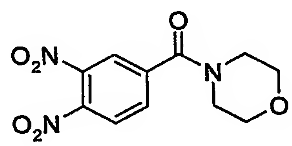


The compound was prepared in a manner analogous to Example 92, but using morpholine as the amine fragment to give 2,6-difluoro-N-[3-(5-hydroxy-4-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (14 mg) as a yellow solid. (LC/MS: R_t 1.82, $[M+H]^+$ 455.13).

EXAMPLE 94

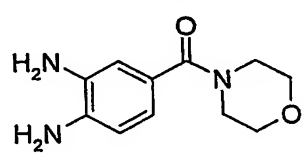
Synthesis of 2,6-Dichloro-N-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide

94A. Synthesis of (3,4-Dinitro-phenyl)-morpholin-4-yl-methanone



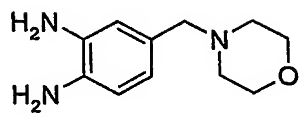
A mixture of 3,4-dinitrobenzoic acid (10.0 g) and thionyl chloride (30 ml) was heated at reflux for 2 hours, cooled to ambient temperature and excess thionyl chloride removed through azeotrope with toluene. The residue was taken up in THF (100 ml) and morpholine (4.1 ml) and Et_3N (7.2 ml) added concurrently to the mixture at 0 °C. The mixture was stirred for 3 hours, water (100 ml) added and then extracted with EtOAc. The organic portion was washed with brine, dried ($MgSO_4$) and reduced *in vacuo*. Recrystallisation of the residue from MeOH gave (3,4-dinitro-phenyl)-morpholin-4-yl-methanone (8.23 g) as a yellow solid. (^{1}H NMR (300 MHz, DMSO-d_6) δ 8.3 (d, 1H), 8.3 (s, 1H), 8.0 (d, 1H), 3.7-3.5 (m, 8H)).

94B. Synthesis of (3,4-Diamino-phenyl)-morpholin-4-yl-methanone



A mixture of (3,4-dinitro-phenyl)-morpholin-4-yl-methanone (1.0 g) and 10% Pd/C (150 mg) in MeOH (30 ml) was shaken under a hydrogen atmosphere at ambient temperature for 10 hours, then filtered through a plug of Celite and reduced *in vacuo* to give (3,4-diamino-phenyl)-morpholin-4-yl-methanone (900 mg). (^{1}H NMR (300 MHz, DMSO-d_6) δ 6.6 (s, 1H), 6.5 (s, 2H), 4.8 (s, 1.5H), 4.6 (s, 1.5H), 4.1 (s, 1H), 3.6 (m, 4H), 3.4 (m, 4H)).

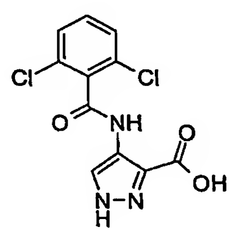
94C. Synthesis of 4-Morpholin-4-ylmethyl-benzene-1,2-diamine



To a mixture of (3,4-dinitro-phenyl)-morpholin-4-yl-methanone (2.84 g) in dry THF (50 ml) was added $NaBH_4$ (954 mg) followed drop-wise by $BF_3.Et_2O$ (3.2 ml). The mixture was stirred at ambient temperature for 3 hours and then quenched though addition of MeOH. The mixture was reduced *in vacuo*, partitioned between EtOAc and water and the organic portion washed with brine, dried ($MgSO_4$) and reduced *in vacuo*. The residue was purified *via* flash column chromatography eluting with EtOAc to give 4-(3,4-dinitro-benzyl)-morpholine (1.08 g).

A mixture of 4-(3,4-dinitro-benzyl)-morpholine (550 mg) and 10% Pd/C (75 mg) in MeOH (10 ml) was shaken under a hydrogen atmosphere at ambient temperature for 4 hours, then filtered through a plug of Celite and reduced *in vacuo* to give 4-morpholin-4-ylmethyl-benzene-1,2-diamine (483 mg) as the major component of a mixture.

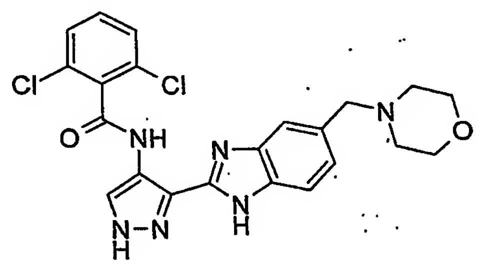
94D. Synthesis of 4-(2,6-Dichloro-benzoylamino)-1H-pyrazole-3-carboxylic acid



Thionyl chloride (0.65 ml) was added to 2,6-dichlorobenzoic acid (825 mg) and the mixture heated at 70 °C for 2 hours. The mixture was allowed to cool and excess thionyl chloride removed through azeotrope with toluene. The residue was taken up in THF (30 ml) and 4-amino-1H-pyrazole-3-carboxylic acid methyl ester (609 mg) and Et_3N (0.75 ml) added concurrently to the mixture at 0 °C. The mixture was stirred for 4 hours, water (100 ml) added and then extracted with EtOAc. The organic portion was washed with brine, dried ($MgSO_4$) and reduced *in vacuo* to give 4-(2,6-dichloro-benzoylamino)-1H-pyrazole-3-carboxylic acid methyl ester (1.23 g) as a red solid. (LC/MS: R_t 3.05, $[M+H]^+$ 313.96).

A mixture of 4-(2,6-dichloro-benzoylamino)-1H-pyrazole-3-carboxylic acid methyl ester (1.21 g) in 2 M aqueous NaOH/MeOH (1:1, 50 ml) was stirred at ambient temperature for 14 hours. Volatile materials were removed *in vacuo*, water (100 ml) added and the mixture taken to pH 5 using 1M aqueous HCl. The resultant precipitate was collected by filtration and dried through azeotrope with toluene to afford 4-(2,6-dichloro-benzoylamino)-1H-pyrazole-3-carboxylic acid as a beige solid (790 mg). (LC/MS: R_t 2.53, $[M+H]^+$ 299.95).

94E. Synthesis of 2,6-Dichloro-N-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide

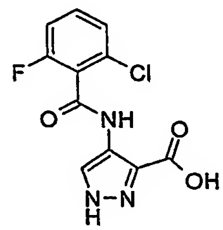


A mixture of 4-(2,6-dichloro-benzoylamino)-1H-pyrazole-3-carboxylic acid (75 mg, 0.25 mmol), 4-morpholin-4-ylmethyl-benzene-1,2-diamine (52 mg, 0.25 mmol), EDC (58 mg, 0.3 mmol) and HOBt (41 mg, 0.3 mmol) in DMF (4 ml) was stirred at ambient temperature for 48 hours. The mixture was partitioned between EtOAc and saturated aqueous $NaHCO_3$ and the organic portion washed with saturated aqueous NH_4Cl, dried ($MgSO_4$) and reduced *in vacuo*. The residue was taken up in AcOH and heated at 100 °C for 14 hours. cooled to ambient temperature and reduced *in vacuo*. The residue was purified *via* flash column chromatography eluting with CH_2Cl_2-MeOH (20:1 – 10:1) to give 2,6-dichloro-N-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (30 mg) as a pink solid. (LC/MS: R_t 2.12, $[M+H]^+$ 471.14).

EXAMPLE 95

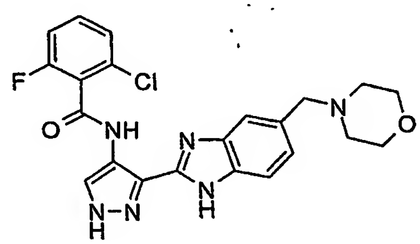
Synthesis of 2-Chloro-6-fluoro-N-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide

95A. Synthesis of 4-(2-Chloro-6-fluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid



The compound was prepared in a manner analogous to 4-(2,6-difluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid (Example 16D), but using 2-chloro-6-fluorobenzoic acid as the starting acid to give 4-(2-chloro-6-fluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid (4.42 g) as a pale blue solid. (LC/MS: R_t 2.35, $[M+H]^+$ 283.94).

95B. Synthesis of 2-Chloro-6-fluoro-N-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide

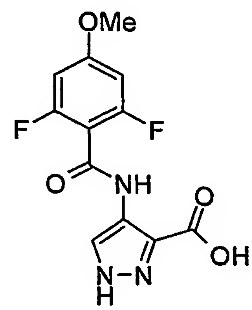


The compound was prepared in a manner analogous to 2,6-dichloro-N-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (Example 94E), but using 4-(2-chloro-6-fluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid, to give 2-chloro-6-fluoro-N-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (37 mg) as a pink solid. (LC/MS: R_t 2.04, $[M+H]^+$ 455.18).

EXAMPLE 96

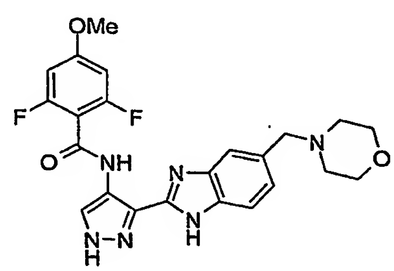
Synthesis of 2,6-Difluoro-4-methoxy-N-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide

96A. Synthesis of 4-(2,6-Difluoro-4-methoxy-benzoylamino)-1H-pyrazole-3-carboxylic acid



The compound was prepared in a manner analogous to 4-(2,6-difluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid (Example 16D), but using 2,6-difluoro-4-methoxybenzoic acid as the starting acid, to give 4-(2,6-difluoro-4-methoxy-benzoylamino)-1H-pyrazole-3-carboxylic acid (1.58 g) as a white solid. (^{1}H NMR (300 MHz, DMSO-d_6) δ 13.0 (s, 2H), 10.7 (s, 1H), 8.0 (s, 1H), 6.9 (s, 1H), 6.8 (s, 1H), 3.7 (s, 3H)).

96B. Synthesis of 2,6-Difluoro-4-methoxy-N-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide

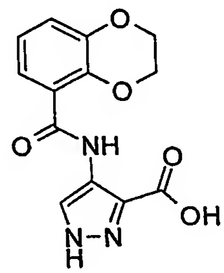


The compound was prepared in a manner analogous to 2,6-dichloro-N-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (Example 94E), but using 4-(2,6-difluoro-4-methoxy-benzoylamino)-1H-pyrazole-3-carboxylic acid to give 2,6-difluoro-4-methoxy-N-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (32 mg) as a pink solid. (LC/MS: R_t 1.99, $[M+H]^+$ 469.21).

EXAMPLE 97

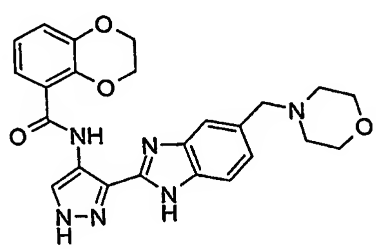
Synthesis of 2,3-Dihydro-benzo[1,4]dioxine-5-carboxylic acid [3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-amide

97A. Synthesis of 4-[(2,3-Dihydro-benzo[1,4]dioxine-5-carbonyl)-amino]-1H-pyrazole-3-carboxylic acid



The compound was prepared in a manner analogous to 4-(2,6-difluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid (Example 16D), but using 2,3-dihydro-benzo[1,4]dioxine-5-carboxylic acid as the starting acid to give 4-[(2,3-dihydro-benzo[1,4]dioxine-5-carbonyl)-amino]-1H-pyrazole-3-carboxylic acid (340 mg) as a white solid. (^{1}H NMR (300 MHz, DMSO-d_6) δ 13.5 (s, 2H), 11.2 (s, 1H), 8.4 (s, 1H), 7.7 (d, 1H), 7.1 (d, 1H), 7.0 (t, 1H), 4.5 (s, 2H), 4.4 (s, 2H)).

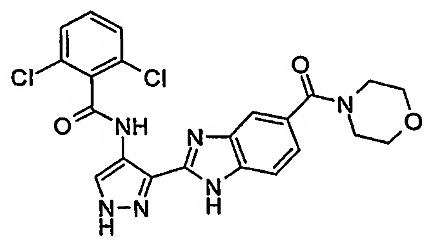
97B. Synthesis of 2,3-Dihydro-benzo[1,4]dioxine-5-carboxylic acid [3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-amide



The compound was prepared in a manner analogous to 2,6-dichloro-N-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (Example 94E), but using 4-[(2,3-dihydro-benzo[1,4]dioxine-5-carbonyl)-amino]-1H-pyrazole-3-carboxylic acid to give 2,3-dihydro-benzo[1,4]dioxine-5-carboxylic acid [3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-amide (39 mg) as a pink solid. (LC/MS: R_t 1.99, $[M+H]^+$ 461.23).

EXAMPLE 98

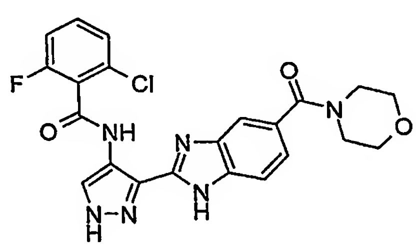
Synthesis of 2,6-Dichloro-N-{3-[5-(morpholine-4-carbonyl)-1H-benzoimidazol-2-yl]-1H-pyrazol-4-yl}-benzamide



The compound was prepared in a manner analogous to 2,6-dichloro-N-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (Example 94E), but using (3,4-diamino-phenyl)-morpholin-4-yl-methanone (Example 94B) to give 2,6-dichloro-N-{3-[5-(morpholine-4-carbonyl)-1H-benzoimidazol-2-yl]-1H-pyrazol-4-yl}-benzamide (17 mg) as a beige solid. (LC/MS: R_t 2.98, $[M+H]^+$ 485.13).

EXAMPLE 99

Synthesis of 2-Chloro-6-fluoro-N-{3-[5-(morpholine-4-carbonyl)-1H-benzoimidazol-2-yl]-1H-pyrazol-4-yl}-benzamide

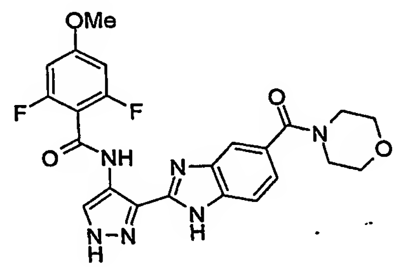


The compound was prepared in a manner analogous to 2,6-dichloro-N-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (Example 94E), but using 4-(2-chloro-6-fluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid (Example 95A) and (3,4-diamino-phenyl)-morpholin-4-yl-methanone (Example 94B) to give 2-chloro-6-fluoro-N-{3-[5-(morpholine-4-

carbonyl)-1H-benzoimidazol-2-yl]-1H-pyrazol-4-yl}-benzamide (18 mg) as a beige solid. (LC/MS: R_t 2.89, $[M+H]^+$ 469.15).

EXAMPLE 100

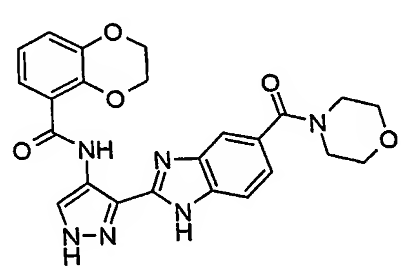
Synthesis of 2,6-Difluoro-4-methoxy-N-{3-[5-(morpholine-4-carbonyl)-1H-benzoimidazol-2-yl]-1H-pyrazol-4-yl}-benzamide



The compound was prepared in a manner analogous to 2,6-dichloro-N-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (Example 94E), however using 4-(2,6-difluoro-4-methoxy-benzoylamino)-1H-pyrazole-3-carboxylic acid (Example 96A) and (3,4-diamino-phenyl)-morpholin-4-yl-methanone (Example 94B) to give 2,6-difluoro-4-methoxy-N-{3-[5-(morpholine-4-carbonyl)-1H-benzoimidazol-2-yl]-1H-pyrazol-4-yl}-benzamide (24 mg) as a beige solid. (LC/MS: R_t 2.94, $[M+H]^+$ 483.20).

EXAMPLE 101

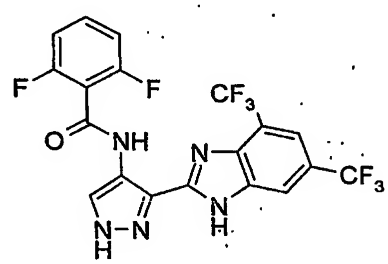
Synthesis of 2,3-Dihydro-benzo[1,4]dioxine-5-carboxylic acid {3-[5-(morpholine-4-carbonyl)-1H-benzoimidazol-2-yl]-1H-pyrazol-4-yl}-amide



The compound was prepared in a manner analogous to 2,6-dichloro-N-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (Example 94E), but using 4-[(2,3-dihydro-benzo[1,4]dioxine-5-carbonyl)-amino]-1H-pyrazole-3-carboxylic acid (Example 97A) and (3,4-diamino-phenyl)-morpholin-4-yl-methanone (Example 94B) to give 2,3-dihydro-benzo[1,4]dioxine-5-carboxylic acid {3-[5-(morpholine-4-carbonyl)-1H-benzoimidazol-2-yl]-1H-pyrazol-4-yl}-amide (15 mg) as a beige solid. (LC/MS: R_t 2.89, $[M+H]^+$ 475.20).

EXAMPLE 102

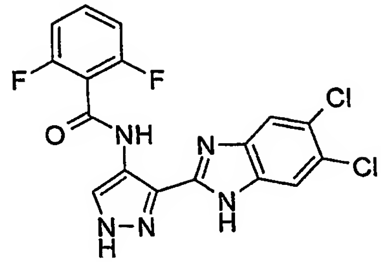
Synthesis of N-[3-(4,6-Bis-trifluoromethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2,6-difluoro-benzamide



The compound was prepared in a manner analogous to 2,6-dichloro-N-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (Example 94E), but using 4-(2,6-difluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid (Example 16D) and 3,5-bis(trifluoromethyl)-1,2-diaminobenzene to give N-[3-(4,6-bis-trifluoromethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2,6-difluoro-benzamide (51 mg) as a pink solid. (LC/MS: R_t 3.64, $[M+H]^+$ 476.07).

EXAMPLE 103

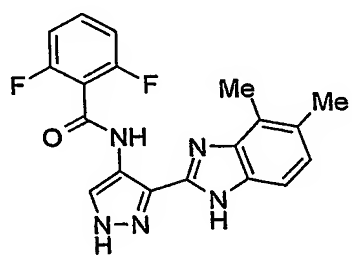
Synthesis of N-[3-(5,6-Dichloro-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2,6-difluoro-benzamide



The compound was prepared in a manner analogous to 2,6-dichloro-N-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (Example 94E), however using 4-(2,6-difluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid (Example 16D) and 4,5-dichloro-1,2-phenylene diamine to give N-[3-(5,6-dichloro-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2,6-difluoro-benzamide (29 mg) as a beige solid. (LC/MS: R_t 3.53, $[M+H]^+$ 408.02).

EXAMPLE 104

Synthesis of N-[3-(4,5-Dimethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2,6-difluoro-benzamide

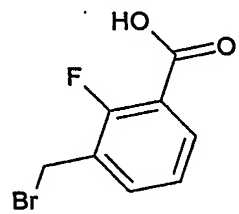


The compound was prepared in a manner analogous to 2,6-dichloro-N-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide (Example 94E), but using 4-(2,6-difluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid (Example 16D) and 3,4-dimethyl-1,2-phenylene diamine to give N-[3-(4,5-dimethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2,6-difluoro-benzamide (89 mg) as a pale orange solid. (LC/MS: R_t 2.98, $[M+H]^+$ 368.15).

EXAMPLE 105

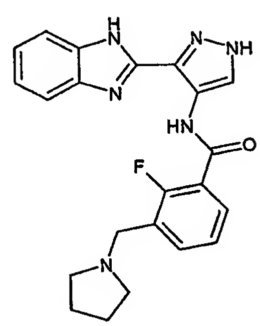
Synthesis of N-[3-(1H-Benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2-fluoro-3-pyrrolidin-1-ylmethyl-benzamide

105A. Synthesis of 3-Bromomethyl-2-fluoro-benzoic acid



A mixture of 2-fluoro-3-methylbenzoic acid (0.462 g, 3 mmol), N-bromosuccinimide (0.560 g, 3.15 mmol), azobisisobutyronitrile (AIBN) (0.024 g, 0.15 mmol) and CCl_4 (10 ml) was heated at reflux for 18 h. The reaction mixture was then reduced *in vacuo* and partitioned between ethyl acetate and aqueous K_2CO_3. The aqueous layer was acidified (2M HCl) and cooled in ice. The precipitate obtained was collected by filtration and dried *in vacuo* to give 3-bromomethyl-2-fluoro-benzoic acid (0.1225 g, 13 %) as a colourless solid. (LC/MS: R_t 3.18, $[M-H]^-$ 232.91).

105B. Synthesis of N-[3-(1H-Benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2-fluoro-3-pyrrolidin-1-ylmethyl-benzamide

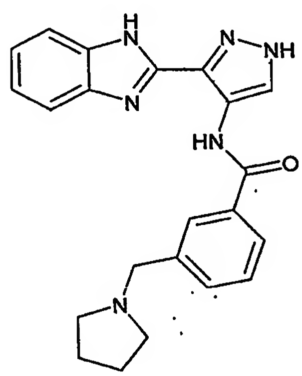


3-Bromomethyl-2-fluoro-benzoic acid (0.058 g, 0.25 mmol) and pyrrolidine (0.036 g, 0.5 mmol) were stirred at ambient temperature for 18 h. The reaction mixture was then azeotroped three times with toluene, acidified with 2M HCl and azeotroped a further three times with toluene to give 2-fluoro-3-pyrrolidin-1-ylmethyl-benzoic acid as its HCl salt. This was combined with 3-(1H-

benzoimidazol-2-yl)-1H-pyrazol-4-ylamine (0.050 g, 0.25 mmol), EDC (0.048 g, 0.25 mmol) and HOBt (0.032 g, 0.25 mmol) and the reaction mixture was stirred at ambient temperature in DMF (0.5 ml) for 20 h. The reaction mixture was purified by preparative LC/MS to give N-[3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-2-fluoro-3-pyrrolidin-1-ylmethyl-benzamide (0.015 g, 15 %) as a brown solid. (LC/MS: R_t 1.79, $[M+H]^+$ 405.13).

EXAMPLE 106

Synthesis of N-[3-(1H-Benzoimidazol-2-yl)-1H-pyrazol-4-yl]-3-pyrrolidin-1-ylmethyl-benzamide



Methyl-3-(bromomethyl)benzoate (0.115 g, 0.5 mmol), pyrrolidine (0.036 g, 0.5 mmol) and K_2CO_3 (0.069 g, 0.5 mmol) were dissolved in DMF (2.5 ml) and stirred at reflux for 18 h. The reaction mixture was the reduced *in vacuo* and subject to column chromatography eluting with hexane ethyl acetate (1:1) to give the crude 3-pyrrolidin-1-ylmethyl-benzoic acid methyl ester, which was added to a solution of LiOH (0.014 g, 0.33 mmol) in 1:1 THF:H_2O (1ml). The reaction mixture was stirred at ambient temperature for 18 h, reduced *in vacuo* and dried through azeotrope with toluene (x3). The resulting solid was dissolved in water (1 ml), acidified with 2M HCl (1 ml), reduced *in vacuo* and dried through azeotrope with toluene (x3) to give a clear, pale yellow gel. This was combined with 3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine (0.050 g, 0.25 mmol), EDC (0.058 g, 0.30 mmol) and HOBt (0.041 g, 0.30 mmol) and the reaction mixture was stirred at ambient temperature in DMSO (0.75 ml) for 64 h. The reaction mixture was purified by preparative LC/MS to give the formate salt of N-[3-(1H-benzoimidazol-

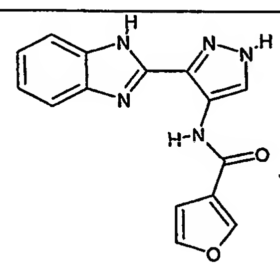
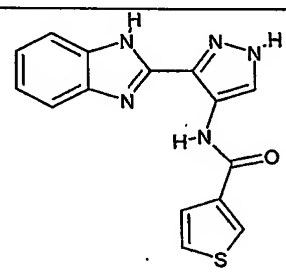
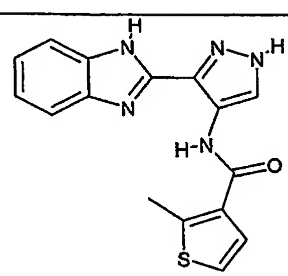
2-yl)-1H-pyrazol-4-yl]-3-pyrrolidin-1-ylmethyl-benzamide (0.018 g, 9 % over 3 steps) as a buff coloured solid. (LC/MS: R_t 1.86, $[M+H]^+$ 387.16).

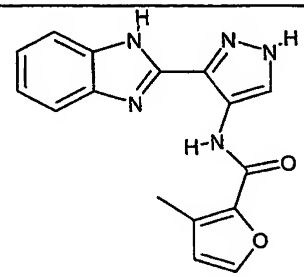
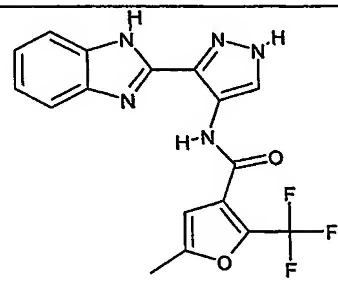
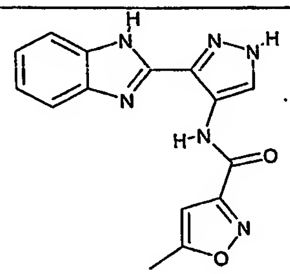
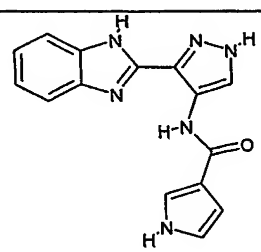
EXAMPLES 107 - 125

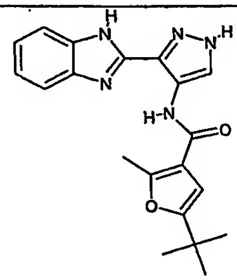
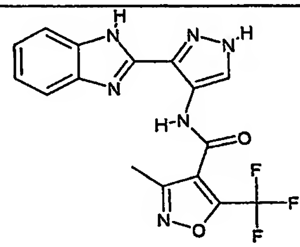
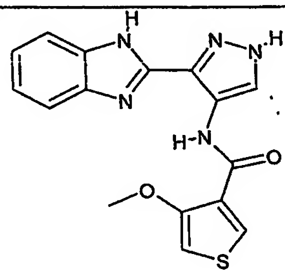
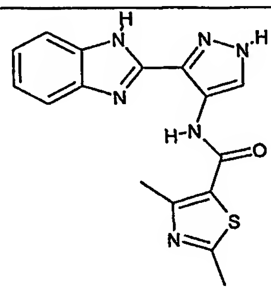
General Procedure D

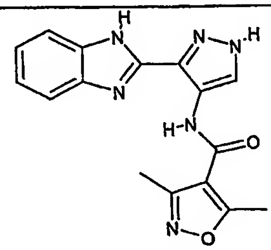
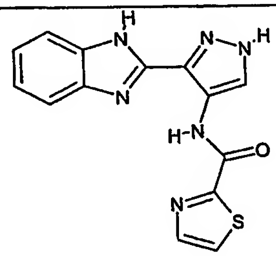
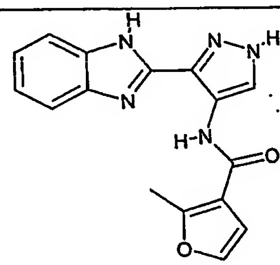
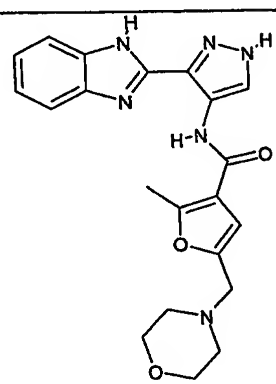
A mixture of the relevant carboxylic acid (1.2 eq.), EDC (1.2 eq.), HOAt (1.2 eq.) in DMSO (1 ml) was added 3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine (50 mg). The reaction was stirred at room temperature for 16 hours. The product was purified by prep HPLC.

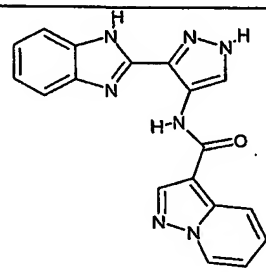
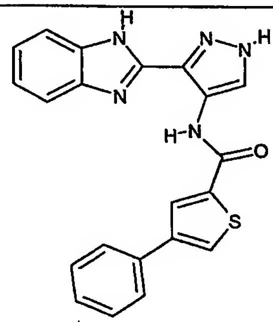
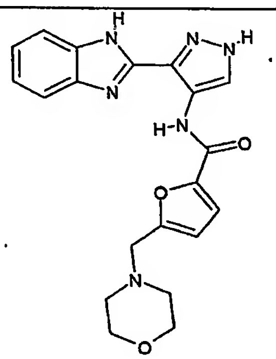
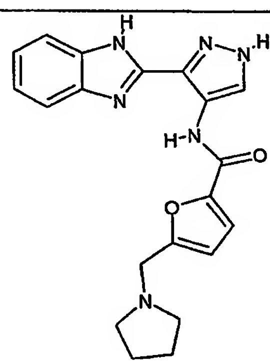
The following compounds were prepared by General Procedure D:

Example	COMPOUND	*m/z* $[M+H]^+$
107		294, RT 3.11 min
108		310, RT 3.48 min
109		324, RT 3.96 min

Example	COMPOUND	*m/z* [M+H]$^+$
110		308, RT 3.54 min
111		376, RT 4.25 min
112		309, RT 3.35 min
113		293, RT 2.40 min

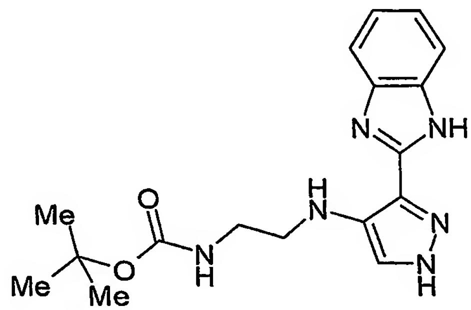
Example	COMPOUND	m/z $[M+H]^+$
114		364, RT 4.94 min
115		377, RT 4.15 min
116		340, RT 3.49 min
117		339, RT 3.35 min

Example	COMPOUND	*m/z* [M+H]$^+$
118		323, RT 2.70 min
119		311, RT 2.55 min
120		308, RT 2.81 min
121		407, RT 1.67 min

Example	COMPOUND	m/z [M+H]$^+$
122		344, RT 2.45 min
123		386, RT 3.47 min
124		393, RT 1.53 min
125		377, RT 1.57 min

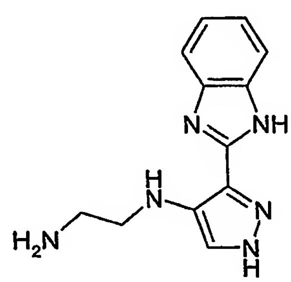
EXAMPLE 126

126A. Synthesis of {2-[3-(1H-Benzoimidazol-2-yl)-1H-pyrazol-4-ylamino}-carbamic acid tert-butyl ester



A mixture of 3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine (250mg, 1.3mmol), acetic acid (108ul, 1.9mmol), sodium triacetoxy borohydride (401mg, 1.9mmol) and tert- butyl-N-(2-oxoethyl) carbamate (301mg, 1.9mmol) in dimethyl formamide (10ml) was stirred at ambient temperature for 4h. The mixture was reduced *in vacuo*. The residue was partitioned between ethyl acetate and sodium hydroxide solution (2N). The organic portion was dried ($MgSO_4$), filtered and reduced *in vacuo* to give 240mg of the title compound as a colourless oil (56%). (LC/MS: R_t 2.59, $[M+H]^+$ 343.19).

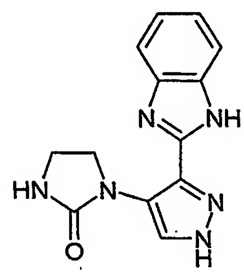
126B Synthesis of N*1*-[3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-ethane-1,2-diamine



{2-[3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamino]-ethyl}-carbamic acid tert-butyl ester (240mg, 0.70 mmol) was dissolved in a mixture of trifluoroacetic acid (5ml) and dichloromethane (5ml) and stirred at ambient temperature for 1h.The

solvent was reduced in vacuo. The residue was dissolved in a mixture of methanol (10ml) and toluene (10ml) and then reduced in vacuo to give 300mg of the title compound as a di trifluoroacetate salt (91%). (LC/MS: Rt 1.86, [M+H]+ 243.11).

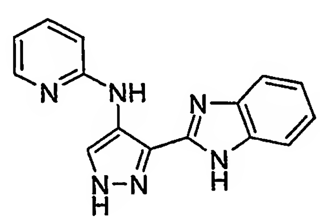
126C. Synthesis of 1-[3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-imidazolidin-2-one



A mixture of N*-1*-[3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-ethane-1,2-diamine (300mg, 0.64 mmol), triethylamine (535ul, 3.84 mmol) and N,N'-carbonyldiimidazole (156mg, 0.96 mmol) in dichloromethane (10ml) was stirred at ambient temperature for 1H. The mixture was the partitioned between ethyl acetate and sodium hydroxide solution (2N). The aqueous was saturated with sodium chloride and washed with ethyl acetate (x2). The organic portions were combined, dried (MgSO4), filtered and reduced in vacuo. The residue was purified by preparative LC/MS and following evaporation of product containing fractions gave 8mg of the title compound as a white solid (5%). (LC/MS: R_t 1.86, $[M+H]^+$ 269.07).

EXAMPLE 127

Synthesis of [3-(1H-Benzoimidazol-2-yl)-1H-pyrazol-4-yl]-pyridin-2-yl-amine,

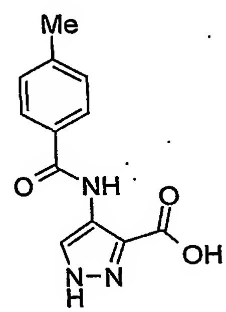


A mixture of 3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-ylamine (150 mg, 0.75 mmol) and 2-fluoropyridine (0.26 ml, 3.0 mmol) was heated in the microwave at 150 °C and 100 W for 15 min. Petroleum ether was added and the solid formed collected by filtration. Recrystallisation from methanol gave [3-(1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-pyridin-2-yl-amine (12 mg). (LC/MS: R_t 0.91, $[M+H]^+$ 277.00).

EXAMPLE 128

Synthesis of N-[3-(5,6-Dimethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-4-methyl-benzamide

128A. Synthesis of 4-(4-Methyl-benzoylamino)-1H-pyrazole-3-carboxylic acid

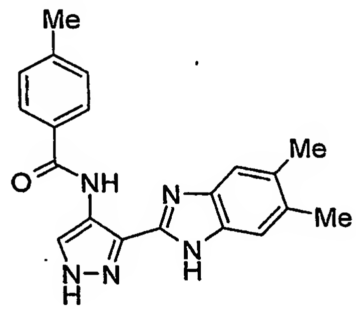


A mixture of p-toluic acid (272 mg), 4-amino-1H-pyrazole-3-carboxylic acid methyl ester (310 mg), EDC (460 mg) and HOBt (324 mg) in DMF (8 ml) was stirred at ambient temperature for 48 h. The mixture was reduced *in vacuo*, partitioned between EtOAc and saturated aqueous $NaHCO_3$ and then the organic portion washed with brine, dried ($MgSO_4$) and reduced *in vacuo* to give 4-(4-methyl-benzoylamino)-1H-pyrazole-3-carboxylic acid methyl ester (486 mg).

A mixture of 4-(4-methyl-benzoylamino)-1H-pyrazole-3-carboxylic acid methyl ester (486 mg) in 2 M aqueous NaOH/MeOH (1:1, 50 ml) was stirred at ambient temperature for 14 h. Volatile materials were removed *in vacuo*, water (100 ml) added and the mixture taken to pH 5 using 2M aqueous HCl. The resultant precipitate was collected by filtration and dried through azeotrope with toluene to

afford 4-(4-methyl-benzoylamino)-1H-pyrazole-3-carboxylic acid as a grey solid (345 mg). (LC/MS: R_t 2.35, $[M+H]^+$ 246.09).

128B. Synthesis of N-[3-(5,6-Dimethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-4-methyl-benzamide



The compound was prepared in a manner analogous to 2,6-dichloro-N-[3-(5-morpholin-4-ylmethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-benzamide, however using 4-(4-methyl-benzoylamino)-1H-pyrazole-3-carboxylic acid and 4,5-dimethylbenzene-1,2-diamine to give N-[3-(5,6-dimethyl-1H-benzoimidazol-2-yl)-1H-pyrazol-4-yl]-4-methyl-benzamide (32 mg) as a white solid. (LC/MS: R_t 3.42, $[M+H]^+$ 346.26).

BIOLOGICAL ACTIVITY

EXAMPLE 129

Measurement of CDK2 Kinase Inhibitory Activity (IC_{50})

Compounds of the invention were tested for kinase inhibitory activity using the following protocol.

1.7 µl of active CDK2/CyclinA (Upstate Biotechnology, 10U/µl) is diluted in assay buffer (250µl of 10X strength assay buffer (200mM MOPS pH 7.2, 250mM β-glycerophosphate, 50mM EDTA, 150mM $MgCl_2$), 11.27 µl 10mM ATP, 2.5 µl 1M DTT, 25 µl 100mM sodium orthovanadate, 708.53 µl H_2O), and 10 µl mixed with 10 µl of histone substrate mix (60 µl bovine histone H1 (Upstate Biotechnology, 5 mg/ml), 940 µl H_2O, 35 µCi $\gamma^{33}P$-ATP) and added to 96 well

plates along with 5 μl of various dilutions of the test compound in DMSO (up to 2.5%). The reaction is allowed to proceed for 5 hours before being stopped with an excess of ortho-phosphoric acid (30 μl at 2%).

γ^{33}P-ATP which remains unincorporated into the histone H1 is separated from phosphorylated histone H1 on a Millipore MAPH filter plate. The wells of the MAPH plate are wetted with 0.5% orthophosphoric acid, and then the results of the reaction are filtered with a Millipore vacuum filtration unit through the wells. Following filtration, the residue is washed twice with 200 μl of 0.5% orthophosphoric acid. Once the filters have dried, 25 μl of Microscint 20 scintillant is added, and then counted on a Packard Topcount for 30 seconds.

The % inhibition of the CDK2 activity is calculated and plotted in order to determine the concentration of test compound required to inhibit 50% of the CDK2 activity (IC_{50}).

The compounds of Examples 3 to 128 each have IC_{50} values of less than 20μM or provide at least 50% inhibition of the CDK2 activity at a concentration of 10μM. Preferred compounds have IC_{50} values of less than 1μM.

EXAMPLE 130

CDK Selectivity Assays

Compounds of the invention were tested for kinase inhibitory activity against a number of different kinases using the general protocol described in Example 129, but modified as set out below.

Kinases are diluted to a 10x working stock in 20mM MOPS pH 7.0, 1mM EDTA, 0.1% γ-mercaptoethanol, 0.01% Brij-35, 5% glycerol, 1mg/ml BSA. One unit equals the incorporation of 1nmol of phosphate per minute into 0.1mg/ml histone H1, or CDK7 substrate peptide at 30 °C with a final ATP concentration of 100uM.

The substrate for all the CDK assays (except CDK7) is histone H1, diluted to 10X working stock in 20mM MOPS pH 7.4 prior to use. The substrate for CDK7 is a specific peptide diluted to 10X working stock in deionised water.

Assay Procedure for CDK1/cyclinB, CDK2/cyclinA, CDK2/cyclinE, CDK3/cyclinE, CDK5/p35, CDK6/cyclinD3:

In a final reaction volume of 25µl, the enzyme (5-10mU) is incubated with 8mM MOPS pH 7.0, 0.2mM EDTA, 0.1mg/ml histone H1, 10mM MgAcetate and [γ-^{33}P-ATP] (specific activity approx 500cpm/pmol, concentration as required). The reaction is initiated by the addition of Mg^{2+} [γ-^{33}P-ATP]. After incubation for 40 minutes at room temperature the reaction is stopped by the addition of 5µl of a 3% phosphoric acid solution. 10ml of the reaction is spotted onto a P30 filter mat and washed 3 times for 5 minutes in 75mM phosphoric acid and once in methanol prior to drying and counting.

Assay procedure for CDK7/cyclinH/MAT1

In a final reaction volume of 25µl, the enzyme (5-10mU) is incubated with 8mM MOPS pH 7.0, 0.2mM EDTA, 500µM peptide, 10mM MgAcetate and [γ-^{33}P-ATP] (specific activity approx 500cpm/pmol, concentration as required). The reaction is initiated by the addition of Mg^2+[γ-^{33}P-ATP]. After incubation for 40 minutes at room temperature the reaction is stopped by the addition of 5µl of a 3% phosphoric acid solution. 10ml of the reaction is spotted onto a P30 filtermat and washed 3 times for 5 minutes in 75mM phosphoric acid and once in methanol prior to drying and counting.

The compounds of Examples 6, 12, 13, 14, 21 and 41 have IC50 values of < 1µM against CDK 1, 3 and 5.

EXAMPLE 131

Anti-proliferative Activity

The anti-proliferative activities of compounds of the invention were determined by measuring the ability of the compounds to inhibition of cell growth in a number of cell lines. Inhibition of cell growth was measured using the Alamar Blue assay (Nociari, M. M, Shalev, A., Benias, P., Russo, C. *Journal of Immunological Methods* 1998, 213, 157-167). The method is based on the ability of viable cells to reduce resazurin to its fluorescent product resorufin. For each proliferation assay cells were plated onto 96 well plates and allowed to recover for 16 hours prior to the addition of inhibitor compounds for a further 72 hours. At the end of the incubation period 10% (v/v) Alamar Blue was added and incubated for a further 6 hours prior to determination of fluorescent product at 535nM ex / 590nM em. In the case of the non-proliferating cell assay cells were maintained at confluence for 96 hour prior to the addition of inhibitor compounds for a further 72 hours. The number of viable cells was determined by Alamar Blue assay as before. All cell lines were obtained from ECACC (European Collection of cell Cultures)..

By following the protocol set out above, compounds of the invention were found to inhibit cell growth in a number of cell lines.

EXAMPLE 132

Measurement of inhibitory activity against Glycogen Synthase Kinase-3 (GSK-3)

GSK3β (human) is diluted to a 10x working stock in 50mM Tris pH 7.5, 0.1mM EGTA, 0.1mM sodium vanadate, 0.1% β-mercaptoethanol, 1mg/ml BSA. One unit equals the incorporation of 1nmol of phosphate per minute phospho-glycogen synthase peptide 2 per minute.

In a final reaction volume of 25μl, GSK3β (5-10 mU) is incubated with 8mM MOPS 7.0, 0.2mM EDTA, 20μM YRRAAVPPSPSLSRHSSPHQS(p)EDEEE (phospho GS2 peptide) , 10mM MgAcetate and [γ-^{33}P-ATP] (specific activity approx 500cpm/pmol, concentration as required). The reaction is initiated by the addition of Mg^{2}+[γ-^{33}P-ATP]. After incubation for 40 minutes at room temperature the reaction is stopped by the addition of 5μl of a 3% phosphoric acid solution. 10μl of the reaction is spotted onto a P30 filter mat and washed 3 times for 5

minutes in 50mM phosphoric acid and once in methanol prior to drying and counting.

The compounds of Examples 6 and 12 have IC50 values of < 1uM against GSK3β.

PHARMACEUTICAL FORMULATIONS

EXAMPLE 133

(i) Tablet Formulation

A tablet composition containing a compound of the formula (I) is prepared by mixing 50mg of the compound with 197mg of lactose (BP) as diluent, and 3mg magnesium stearate as a lubricant and compressing to form a tablet in known manner.

(ii) Capsule Formulation

A capsule formulation is prepared by mixing 100mg of a compound of the formula (I) with 100mg lactose and filling the resulting mixture into standard opaque hard gelatin capsules.

EXAMPLE 134

Determination of Antifungal Activity

The antifungal activity of the compounds of the formula (I) is determined using the following protocol.

The compounds are tested against a panel of fungi including Candida parpsilosis, Candida tropicalis, Candida albicans-ATCC 36082 and Cryptococcus neoformans. The test organisms are maintained on Sabourahd Dextrose Agar slants at 4 °C. Singlet suspensions of each organism are prepared by growing the yeast overnight at 27 °C on a rotating drum in yeast-nitrogen base broth (YNB) with amino acids (Difco, Detroit, Mich.), pH 7.0 with 0.05 M morpholine propanesulphonic acid (MOPS). The suspension is then centrifuged and washed twice with 0.85% NaCl before sonicating the washed cell suspension for 4 seconds (Branson Sonifier,

model 350, Danbury, Conn.). The singlet blastospores are counted in a haemocytometer and adjusted to the desired concentration in 0.85% NaCl.

The activity of the test compounds is determined using a modification of a broth microdilution technique. Test compounds are diluted in DMSO to a 1.0 mg/ml ratio then diluted to 64 μg/ml in YNB broth, pH 7.0 with MOPS (Fluconazole is used as the control) to provide a working solution of each compound. Using a 96-well plate, wells 1 and 3 through 12 are prepared with YNB broth, ten fold dilutions of the compound solution are made in wells 2 to 11 (concentration ranges are 64 to 0.125 μg/ml). Well 1 serves as a sterility control and blank for the spectrophotometric assays. Well 12 serves as a growth control. The microtitre plates are inoculated with 10 μl in each of well 2 to 11 (final inoculum size is 10^4 organisms/ml). Inoculated plates are incubated for 48 hours at 35 °C. The IC50 values are determined spectrophotometrically by measuring the absorbance at 420 nm (Automatic Microplate Reader, DuPont Instruments, Wilmington, Del.) after agitation of the plates for 2 minutes with a vortex-mixer (Vorte-Genie 2 Mixer, Scientific Industries, Inc., Bolemia, N.Y.). The IC50 endpoint is defined as the lowest drug concentration exhibiting approximately 50% (or more) reduction of the growth compared with the control well. With the turbidity assay this is defined as the lowest drug concentration at which turbidity in the well is <50% of the control (IC50). Minimal Cytolytic Concentrations (MCC) are determined by sub-culturing all wells from the 96-well plate onto a Sabourahd Dextrose Agar (SDA) plate, incubating for 1 to 2 days at 35 °C and then checking viability.

EXAMPLE 135

Protocol for the Biological Evaluation of Control of in vivo Whole Plant Fungal Infection

Compounds of the formula (I) are dissolved in acetone, with subsequent serial dilutions in acetone to obtain a range of desired concentrations. Final treatment volumes are obtained by adding 9 volumes of 0.05% aqueous Tween-20 ™ or 0.01% Triton X-100™, depending upon the pathogen.

The compositions are then used to test the activity of the compounds of the invention against tomato blight (Phytophthora infestans) using the following protocol. Tomatoes (cultivar Rutgers) are grown from seed in a soil-less peat-based potting mixture until the seedlings are 10-20 cm tall. The plants are then sprayed to run-off with the test compound at a rate of 100 ppm. After 24 hours the test plants are inoculated by spraying with an aqueous sporangia suspension of Phytophthora infestans, and kept in a dew chamber overnight. The plants are then transferred to the greenhouse until disease develops on the untreated control plants.

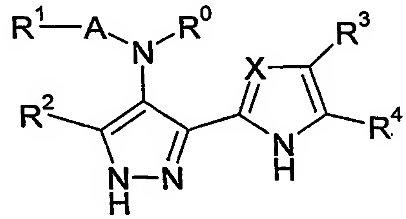
Similar protocols are also used to test the activity of the compounds of the invention in combatting Brown Rust of Wheat (Puccinia), Powdery Mildew of Wheat (Ervsiphe vraminis), Wheat (cultivar Monon), Leaf Blotch of Wheat (Septoria tritici), and Glume Blotch of Wheat (Leptosphaeria nodorum).

Equivalents

The foregoing examples are presented for the purpose of illustrating the invention and should not be construed as imposing any limitation on the scope of the invention. It will readily be apparent that numerous modifications and alterations may be made to the specific embodiments of the invention described above and illustrated in the examples without departing from the principles underlying the invention. All such modifications and alterations are intended to be embraced by this application.

CLAIMS

1. The use of a compound for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by a cyclin dependent kinase or glycogen synthase kinase-3, the compound having the formula (I):



wherein

X is CR^5 or N;

A is a bond or $-(CH_2)_m-(B)_n-$;

B is C=O, $NR^g(C=O)$ or O(C=O) wherein R^g is hydrogen or C_{1-4} hydrocarbyl optionally substituted by hydroxy or C_{1-4} alkoxy;

m is 0, 1 or 2;

n is 0 or 1;

R^0 is hydrogen or, together with NR^g when present, forms a group $-(CH_2)_p-$ wherein p is 2 to 4;

R^1 is hydrogen, a carbocyclic or heterocyclic group having from 3 to 12 ring members, or an optionally substituted C_{1-8} hydrocarbyl group;

R^2 is hydrogen, halogen, methoxy, or a C_{1-4} hydrocarbyl group optionally substituted by halogen, hydroxyl or methoxy;

R^3 and R^4 together with the carbon atoms to which they are attached form an optionally substituted fused carbocyclic or heterocyclic ring having from 5 to 7 ring members of which up to 3 can be heteroatoms selected from N, O and S; and

R^5 is hydrogen, a group R^2 or a group R^{10} wherein R^{10} is selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups

having from 3 to 12 ring members; a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^c, SO_2NR^c or NR^cSO_2; and R^b is selected from hydrogen, carbocyclic and heterocyclic groups having from 3 to 12 ring members, and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

R^c is selected from hydrogen and C_{1-4} hydrocarbyl; and

X^1 is O, S or NR^c and X^2 is =O, =S or $=NR^c$.

2. The use according to claim 1 wherein X is N.

3. The use according to claim 1 wherein X is CH.

4. The use according to any one of claims 1 to 3 wherein B is C=O or $NR^g(C{=}O)$, m is 0, 1 or 2; and n is 0 or 1.

5. The use according to claim 4 wherein m is 0 or 1 (preferably 0), n is 1 and B is C=O.

6. The use according to any one of the preceding claims wherein R^0 is hydrogen.

7. The use according to any one of the preceding claims wherein B is $NR^g(C{=}O)$ and R^g is hydrogen.

8. The use according to any one of the preceding claims wherein R^1 is a carbocyclic or heterocyclic group having from 3 to 12 ring members.

9. The use according to claim 8 wherein the carbocyclic or heterocyclic group is monocyclic or bicyclic.

10. The use according to claim 8 or claim 9 wherein the carbocyclic or heterocyclic group is an aryl or heteroaryl group.

11. The use according to claim 10 wherein the aryl and heteroaryl groups are selected from pyridine, pyrrole, furan, thiophene, imidazole, oxazole, oxadiazole, oxatriazole, isoxazole, thiazole, isothiazole, pyrazole, pyrazine, pyridazine, pyrimidine, triazine, triazole, tetrazole, quinoline, isoquinoline, benzfuran, benzthiophene, chroman, thiochroman, benzimidazole, benzoxazole, benzisoxazole, benzthiazole, benzisothiazole, isobenzofuran, indole, isoindole, indolizine, indoline, isoindoline, purine (e.g., adenine, guanine), indazole, benzodioxole, chromene, isochromene, chroman, isochroman, benzodioxan, quinolizine, benzoxazine, benzodiazine, pyridopyridine, pyrazolopyridine, quinoxaline, quinazoline, cinnoline, phthalazine, naphthyridine and pteridine, tetrahydronaphthalene, tetrahydroisoquinoline, tetrahydroquinoline, dihydrobenzthiene, dihydrobenzfuran, 2,3-dihydro-benzo[1,4]dioxine, benzo[1,3]dioxole, 4,5,6,7-tetrahydrobenzofuran, indoline, indane, phenyl, naphthyl, indenyl, and tetrahydronaphthyl groups.

12. The use according to claim 11 wherein the aryl and heteroaryl groups are selected from pyrazolo[1,5-a]pyridinyl (e.g. pyrazolo[1,5-a]pyridin-3-yl), furanyl (e.g. 2-furanyl and 3-furanyl), indolyl (e.g. 3-indolyl, 4-indolyl and 7-indolyl), oxazolyl, thiazolyl (e.g. thiazol-2-yl and thiazol-5-yl), isoxazolyl (e.g. isoxazol-3-yl and isoxazol-4-yl), pyrrolyl (e.g. 3-pyrrolyl), pyridyl (e.g. 2-pyridyl), quinolinyl (e.g. quinolin-8-yl), 2,3-dihydro-benzo[1,4]dioxine (e.g. 2,3-dihydro-benzo[1,4]dioxin-5-yl), benzo[1,3]dioxole (e.g. benzo[1,3]dioxol-4-yl), 2,3-dihydrobenzofuranyl (e.g. 2,3-dihydrobenzofuran-7-yl), imidazolyl and thiophenyl (e.g. 3-thiophenyl) groups.

13. The use according to claim 12 wherein the aryl and heteroaryl groups are selected from phenyl, pyrazolo[1,5-a]pyridinyl, furanyl, 2,3-

dihydrobenzofuranyl, thiophenyl, indolyl, thiazolyl, isoxazolyl and 2,3-dihydro-benzo[1,4]dioxine groups.

14. The use according to claim 11 wherein the aryl and heteroaryl groups are selected from phenyl, furanyl, indolyl, oxazolyl, isoxazolyl, pyridyl, quinolinyl, 2,3-dihydro-benzo[1,4]dioxine, benzo[1,3]dioxole, imidazolyl and thiophenyl groups.

15. The use according to claim 14 wherein R^1 is a substituted or unsubstituted phenyl ring.

16. The use according to claim 8 or claim 9 wherein R^1 is a non-aromatic group selected from monocyclic cycloalkyl groups and azacycloalkyl groups such as cyclohexyl, cyclopentyl, and piperidinyl.

17. The use according to any one of claims 8 to 16 wherein the carbocyclic or heterocyclic group R^1 is an unsubstituted group.

18. The use according to any one of claims 8 to 16 wherein the carbocyclic or heterocyclic group R^1 bears one or more substituents selected from the group R^{10} as defined in claim 1.

19. The use according to claim 18 wherein the substituents on R^1 are selected from the group R^{10a} consisting of halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, heterocyclic groups having 5 or 6 ring members and up to 2 heteroatoms selected from O, N and S, a group R^a-R^b wherein R^a is a bond, O, CO, $X^3C(X^4)$, $C(X^4)X^3$, $X^3C(X^4)X^3$, S, SO, or SO_2, and R^b is selected from hydrogen, heterocyclic groups having 5 or 6 ring members and up to 2 heteroatoms selected from O, N and S, and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having 5 or 6 ring members and up to 2 heteroatoms selected from O, N and S; wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be

replaced by O, S, SO, SO_2, $X^3C(X^4)$, $C(X^4)X^3$ or $X^3C(X^4)X^3$; X^3 is O or S; and X^4 is =O or =S.

20. The use according to claim 19 wherein the substituents on R^1 are selected from the group R^{10b} consisting of halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, a group R^a-R^b wherein R^a is a bond, O, CO, $X^3C(X^4)$, $C(X^4)X^3$, $X^3C(X^4)X^3$, S, SO, or SO_2, and R^b is selected from hydrogen and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy; wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, $X^3C(X^4)$, $C(X^4)X^3$ or $X^3C(X^4)X^3$; X^3 is O or S; and X^4 is =O or =S.

21. The use according to claim 18 wherein the substituents on R^1 are selected from halogen, hydroxy, trifluoromethyl, a group R^a-R^b wherein R^a is a bond or O, and R^b is selected from hydrogen and a C_{1-4} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxyl and halogen.

22. The use according to any one of claims 18 to 21 wherein R^1 is substituted by 1 or 2 or 3 or 4 substituents.

23. The use according to claim 22 wherein R^1 is a phenyl group which is 2,6-disubstituted, 2,3-disubstituted, 2,4-disubstituted 2,5-disubstituted, 2,3,6-trisubstituted or 2,4,6-trisubstituted.

24. The use according to claim 23 wherein R^1 is a phenyl group which is disubstituted at positions 2- and 6- with substituents selected from fluorine, chlorine and R^a-R^b, where R^a is O and R^b is C_{1-4} alkyl.

25. The use according to any one of the preceding claims wherein R^1 is any one group selected from groups A1 to A60 set out in Table 1 herein.

26. The use according to claim 25 wherein R^1 is any one group selected from groups A1 to A34 in Table 1.

27. The use according to claim 26 wherein R^1 is selected from 2,6-difluorophenyl, 2-chloro-6-fluorophenyl, 2-fluoro-6-methoxyphenyl, 2,6-dichlorophenyl, 2,4,6-trifluorophenyl, 2-chloro-6-methyl, 2,3-dihydro-benzo[1,4]dioxin-5-yl and pyrazolo[1,5-a]pyridin-3-yl.

28. The use according to claim 27 wherein R^1 is 2,6-difluorophenyl.

29. The use according to any one of the preceding claims wherein R^2 is hydrogen, chlorine or methyl, and most preferably R^2 is hydrogen.

30. The use according to any one of the preceding claims wherein R^3 and R^4, together with the carbon atoms to which they are attached, form a fused aromatic heterocyclic or carbocyclic group having from 5 to 7 ring members.

31. The use according to claim 30 wherein R^3 and R^4 together with the carbon atoms to which they are attached form a fused carbocyclic group.

32. The use according to claim 31 wherein the fused carbocyclic group is selected from benzo, dihydro or tetrahydro-benzo and cyclopenta- fused rings.

33. The use according to claim 32 wherein the fused carbocyclic group is a benzo group

34. The use according to claim 30 wherein R^3 and R^4 together with the carbon atoms to which they are attached form a fused heterocyclic rings selected from thiazolo, isothiazolo, oxazolo, isoxazolo, pyrrolo, pyrido, thieno, furano, pyrimido, pyrazolo, pyrazino, and imidazolo fused rings.

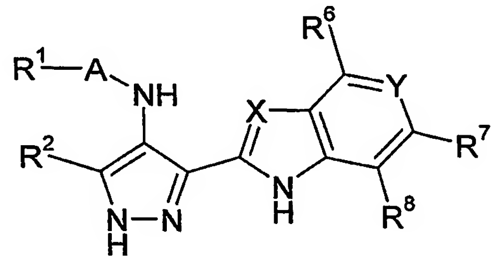
35. The use according to claim 34 wherein the fused heterocyclic group is a pyrido group.

36. The use according to any one of the preceding claims wherein the fused carbocyclic or heterocyclic ring formed by R^3 and R^4 and the carbon atoms to which they are attached is substituted by up 4 groups R^{10} as defined in claim 1.

37. The use according to claim 36 wherein the substituents on the fused carbocyclic or heterocyclic group are selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, monocyclic carbocyclic and heterocyclic groups having from 3 to 7 (typically 5 or 6) ring members, a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^c, SO_2NR^c or NR^cSO_2; and R^b is selected from hydrogen, a carbocyclic or heterocyclic group with 3-7 ring members and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, a carbocyclic or heterocyclic group with 3-7 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$; and R^c, X^1 and X^2 are as hereinbefore defined, or two adjacent groups R^{10} together with the carbon atoms or heteroatoms to which they are attached may form a 5-membered heteroaryl ring or a 5- or 6-membered non-aromatic heterocyclic ring, wherein the said heteroaryl and heterocyclic groups contain up to 3 heteroatom ring members selected from N, O and S.

38. The use according to claim 37 wherein the R^{10} group or groups on the fused carbocyclic or heterocyclic group formed by R^3 and R^4 are selected from halogen, nitro, carboxy, a group R^a-R^b wherein R^a is a bond, O, CO, $C(X^2)X^1$, and R^b is selected from hydrogen, heterocyclic group having 3-7 ring members and a C_{1-4} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, heterocyclic group with 3-7 ring members.

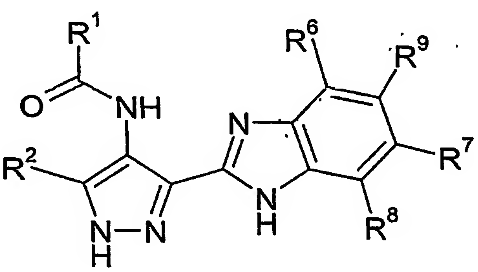
39. The use according to any one of the preceding claims wherein the compound is a compound of the formula (II):



(II)

wherein Y is N or CR^9 wherein R^9 is hydrogen or a group R^{10}; and R^6, R^7 and R^8 are the same or different and each is hydrogen or a group R^{10}.

40. The use according to any one of the preceding claims wherein the compound is a compound of the formula (III):



(III)

41. The use according to claim 40 wherein R^6, R^7, R^8 and R^9 are selected from hydrogen, halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, monocyclic carbocyclic and heterocyclic groups having from 3 to 12 (preferably 3 to 7, and more typically 5 or 6) ring members, a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^c, SO_2NR^c or NR^cSO_2; and R^b is selected from hydrogen, a carbocyclic or heterocyclic group with 3-7 ring members and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, C_{1-4} acyloxy, oxo, halogen, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, a carbocyclic or heterocyclic

group with 3-7 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$; and R^c, X^1 and X^2; or an adjacent pair of substituents selected from R^6, R^7, R^8 and R^9 together with the carbon atoms to which they are attached may form a non-aromatic five or six membered ring containing up to three heteroatoms selected from O, N and S.

42. The use according to claim 41 wherein R^6 to R^9 are each hydrogen or are selected from halogen, cyano, hydroxy, trifluoromethyl, nitro, a group R^a-R^b wherein R^a is a bond, O, CO or $C(X^2)X^1$ and R^b is selected from hydrogen, heterocyclic groups having from 3 to 12 ring members (preferably 4 to 7 ring members), and a C_{1-8} hydrocarbyl group (preferably a C_{1-4} hydrocarbyl group), optionally substituted by one or more substituents selected from hydroxy, C_{1-4} acyloxy, mono- or di-C_{1-4} hydrocarbylamino, heterocyclic groups having from 3 to 12 ring members, more preferably 4 to 7 ring members; where R^c is selected from hydrogen and C_{1-4} hydrocarbyl, X^1 is O or NR^c and X^2 is =O.

43. The use according to claim 41 wherein R^6, R^7, R^8 and R^9 are selected from hydrogen, fluorine, chlorine, bromine, nitro, trifluoromethyl, carboxy, a group R^a-R^b wherein R^a is a bond, O, CO, $C(X^2)X^1$, and R^b is selected from hydrogen, heterocyclic groups having 3-7 ring members (e.g. pyrrolidine, N-methyl piperazine or morpholine) and a C_{1-4} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, carboxy, C_{1-4} acyloxy, amino, mono- or di-C_{1-4} hydrocarbylamino, heterocyclic groups with 3-7 ring members (e.g. pyrrolidine, N-methyl piperazine or morpholine); or an adjacent pair of substituents selected from R^6, R^7, R^8 and R^9 together with the carbon atoms to which they are attached may form a non-aromatic five or six membered ring containing one or two oxygen atoms as ring members.

44. The use according to claim 41 wherein R^6, R^7, R^8 and R^9 are selected from hydrogen, fluorine, chlorine, trifluoromethyl, a group R^a-R^b wherein R^a is a bond, O, CO, $C(X^2)X^1$, and R^b is selected from hydrogen, saturated heterocyclic groups having 5-6 ring members and a C_{1-2} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, carboxy, C_{1-2} acyloxy, amino, mono- or di-C_{1-4} hydrocarbylamino, heterocyclic groups with 5-6 ring members; or an adjacent pair of substituents selected from R^6, R^7, R^8 and R^9 may form a methylenedioxy or ethylenedioxy group each optionally substituted by one or more fluorine atoms.

45. The use according to claim 41 wherein R^6 to R^9 are selected from hydrogen, halogen, nitro, carboxy, a group R^a-R^b wherein R^a is a bond, O, CO, $C(X^2)X^1$, and R^b is selected from hydrogen, heterocyclic group having 3-7 ring members and a C_{1-4} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, heterocyclic group with 3-7 ring members.

46. The use according to any one of claims 40 to 45 wherein at least one, and more preferably at least two, of R^6 to R^9 are hydrogen.

47. The use according to claim 46 wherein one of R^6 to R^9 is a substituent and the others each are hydrogen.

48. The use according to claim 47 wherein R^6 is a substituent group and R^7 to R^9 are each hydrogen

49. The use according to claim 47 wherein R^9 is a substituent and R^6, R^7 and R^8 are each hydrogen.

50. The use according to claim 46 wherein two of R^6 to R^9 are substituents and the other two both are hydrogen.

51. The use according to claim 50 wherein R^6 and R^9 are both substituents and R^7 and R^8 both are hydrogen.

52. The use according to claim 50 wherein R^6 and R^7 both are substituents and R^8 and R^9 are both hydrogen.

53. The use according to claim 50 wherein R^7 and R^9 both are substituents and R^6 and R^8 are both hydrogen.

54. The use according to any one of claims 40 to 53 wherein R^6 is selected from:
hydrogen;
halogen (preferably fluorine or chlorine);
methyl optionally substituted by a substituent selected from hydroxy, halogen (e.g. fluorine, preferably difluoro or trifluoro, and more preferably trifluoro) and $NR^{11}R^{12}$; and
$C(=O)NR^{11}R^{12}$;
wherein R^{11} and R^{12} are the same or different and each is selected from hydrogen and C_{1-4} alkyl or R^{11} and R^{12} together with the nitrogen atom form a five or six membered heterocyclic ring having 1 or 2 heteroatom ring members selected from O, N and S (preferably O and N).

55. The use according to anyone of claims 40 to 54 wherein R^7 is selected from:
hydrogen;
halogen (preferably fluorine or chlorine);
C_{1-4} alkoxy (for example methoxy);
methyl optionally substituted by a substituent selected from hydroxy, halogen (e.g. fluorine, preferably difluoro or trifluoro, and more preferably trifluoro) and $NR^{11}R^{12}$; and
$C(=O)NR^{11}R^{12}$;
wherein R^{11} and R^{12} are the same or different and each is selected from hydrogen and C_{1-4} alkyl or R^{11} and R^{12} together with the nitrogen atom

form a five or six membered heterocyclic ring having 1 or 2 heteroatom ring members selected from O, N and S (preferably O and N).

56. The use according to any one of claims 40 to 55 wherein R^8 is selected from hydrogen, fluorine and methyl, most preferably hydrogen.

57. The use according to any one of claims 40 to 56 wherein R^9 is selected from:

hydrogen;

halogen (preferably fluorine or chlorine);

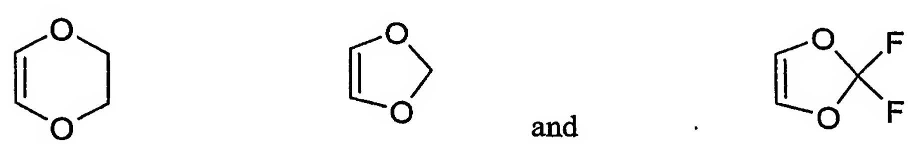
C_{1-4} alkoxy (for example methoxy);

methyl optionally substituted by a substituent selected from hydroxy, halogen (e.g. fluorine, preferably difluoro or trifluoro, and more preferably trifluoro) and $NR^{11}R^{12}$; and

$C(=O)NR^{11}R^{12}$;

wherein R^{11} and R^{12} are the same or different and each is selected from hydrogen and C_{1-4} alkyl or R^{11} and R^{12} together with the nitrogen atom form a five or six membered heterocyclic ring having 1 or 2 heteroatom ring members selected from O, N and S (preferably O and N).

58. The use according to claim 40 wherein R^6 and R^9, or R^7 and R^9, together with the carbon atoms to which they are attached form a cyclic group selected from:



59. The use according to any one of claims 54, 55 and 57 wherein R^{11} and R^{12} together with the nitrogen atom in the group $NR^{11}R^{12}$ form a five or six membered heterocyclic ring, the heteroatom ring members being preferably selected from O and N.

60. The use according to claim 59 wherein the heterocyclic ring is non-aromatic and, for example, is selected from morpholine, piperazine, N-C_{1-4}-alkylpiperazine, piperidine and pyrrolidine.

61. The use according to any one of the preceding claims wherein R^3 and R^4 together with the carbon atoms to which they are attached form a benzimidazole group selected from the groups B1 to B47 in Table 2 herein.

62. The use according to claim 61 wherein the benzimidazole group is selected from the groups B1, B3, B5-B8, B11-B20, B23-B30 and B32-B47 in Table 2.

63. The use according to claim 62 wherein the benzimidazole group is selected from the groups B1, B3, B5-B8, B11-B20, B24, B25, B27-B30 and B32-B47 in Table 2.

64. The use according to any one of the preceding claims wherein the compound of the formula (I) is as illustrated in the Examples herein.

65. The use according to any one of the preceding claims wherein the compound is in the form of a salt or solvate.

66. A method for the prophylaxis or treatment of a disease state or condition mediated by a cyclin dependent kinase, which method comprises administering to a subject in need thereof a compound of the formula (I) as defined in any one of claims 1 to 65.

67. A method of inhibiting a cyclin dependent kinase, which method comprises contacting the kinase with a kinase-inhibiting compound of the formula (I) as defined in any one of claims 1 to 65.

68. A method of modulating a cellular process (for example cell division) by inhibiting the activity of a cyclin dependent kinase using a compound of the formula (I) as defined in any one of claims 1 to 65.

69. A method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, which method comprises administering to the mammal a compound of formula (I) as defined in any one of claims 1 to 65 in an amount effective in inhibiting abnormal cell growth.

70. A method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, the method comprising administering to the mammal a compound of formula (I) as defined in any one of claims 1 to 65 in an amount effective to inhibit cdk2 activity.

71. A compound of the formula (I) as defined in any one of claims 1 to 65 for use in the prophylaxis or treatment of a disease state or condition mediated by glycogen synthase kinase-3.

72. The use of a compound of the formula (I) as in any one of claims 1 to 65 for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by glycogen synthase kinase-3.

73. A method for the prophylaxis or treatment of a disease state or condition mediated by glycogen synthase kinase-3, which method comprises administering to a subject in need thereof a compound of the formula (I) as defined in any one of claims 1 to 65.

74. A method of inhibiting glycogen synthase kinase-3, which method comprises contacting the kinase with a kinase-inhibiting compound of the formula (I) as defined in any one of claims 1 to 65.

75. A method of modulating a cellular process (for example cell division) by inhibiting the activity of glycogen synthase kinase-3 using a compound of the formula (I) as defined in any one of claims 1 to 65

76. A method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, the method comprising administering

to the mammal a compound of formula (I) as defined in any one of claims 1 to 65 in an amount effective to inhibit glycogen synthase kinase-3 activity.

77. A use or method as defined in any one of the preceding claims wherein the disease state or condition is selected from proliferative disorders such as cancers and conditions such as viral infections, autoimmune diseases and neurodegenerative diseases.

78. A use or method according to claim 77 wherein the disease state is a cancer selected from breast cancer, ovarian cancer, colon cancer, prostate cancer, oesophageal cancer, squamous cancer, and non-small cell lung carcinomas.

79. The use of a compound as defined in any one of claims 1 to 65 for the manufacture of a medicament for the treatment or prophylaxis of a fungal infection in an animal.

80. A method for the treatment or prophylaxis of a fungal infection in an animal or plant comprising administering to the animal or plant an effective antifungal amount of a compound of the formula (I) as defined in any one of claims 1 to 65.

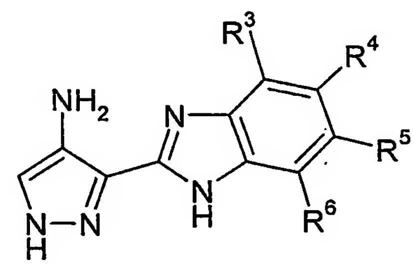
81. A compound *per se*, said compound being a compound of the formula (I) as defined in any one of claims 1 to 65.

82. A compound according to claim 81, wherein the group R^1 is a pyrazolopyridine group, for example, a pyrazolo[1,5-a]pyridine group, such as a 3-pyrazolo[1,5-a]pyridinyl group.

83. A compound according to claim 81 wherein R^1 is selected from groups A29, A35 and A36 in table 1.

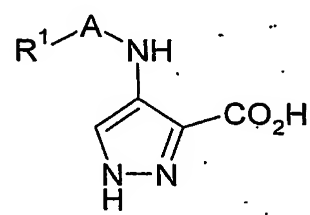
84. A process for the preparation of a compound as defined in any one of claims 1 to 65 and 81 to 83, which process comprises:

(i) the reaction of a compound of the formula:

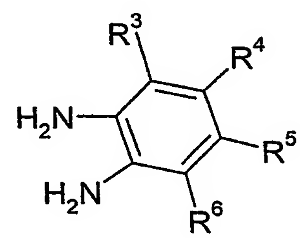


with a compound of the formula R^1-A' wherein A' is an isocyanate group N=C=O, or a group CO_2H or an activated derivative thereof; or

(ii) the reaction of a compound of the formula:



with a diamine compound of the formula:



wherein R^1 and R^3 to R^6 are as defined in any one of the preceding claims; and optionally thereafter converting one compound of the formula (I) into another compound of the formula (I).

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